Date: October 11, 2001

To: Hospital Emergency Room Directors
Emergency Room Physicians
Urgent Care, Clinic, and Primary Care Physicians
Laboratory Directors
Emergency Medical Services Personnel

From: Richard J. Burton, M.D., M.P.H., Health Officer and
Mark J. Miller, P.H.M., C.M.S., Director of Communicable Disease Control

Re: RECOGNIZING BIOTERRORISM AGENTS

It is crucial that emergency room physicians and other clinicians have a clear understancing of how to recognize a patient presenting with possible exposure to a biological agent that may be used by terrorists. Although this situation has not presented in Placer County, there are truly dire consequences of not recognizing a potential incident and reporting it to the Public Health Department.

We all remember the medical school adage, " When you hear hoofbeats, think horses, not zebras." But now, the public health and medical community is challenged by the threat of bioterrorism incidents. It is vital that we learn how to recognize a zebra among the horses by increasing awareness of the clinical syndromes of each potential bioterrorism agent.

The Zebra Packet is designed to assist you in responding properly to a possible patient exposure. The Public Health Department is distributing the enclosed materials to all local emergency rooms in order to maintain a written guideline for use by emergency departments, clinics, and primary care clinicians. We hope you will post the laminated disease cards in your offices. We will provide additional information that can be inserted into the Zebra Packet binder as it becomes available.

In the Zebra Packet you will find:

1. Public Health Department Reporting Instructions
2. Laminated Disease Syndrome Cards for the six primary agents of bioterrorism
3. Reference material

If you have additional questions, please call the Health and Human Services, Communicable Disease Control office at (530) 889-7141. After hours call: Health Officer, Richard J. Burton, M.D., M.P.H., at (530) 889-7119.

DETECTING BIOTERRORISM
The Clinician's Role

Health care providers will be "first responders" in the event of a bioterrorism attack or other public health emergency. **Early detection by astute clinicians and rapid reporting to the local health department will be critical** in minimizing the impact of a bioterrorism event or other disaster.

Bioterrorism attacks are likely to present as acute outbreaks of an unusual syndrome, or outbreak of illnesses in the "wrong" season, or geographic area.

If you see patient(s) with any of the following clinical syndromes:

1. Acute severe pneumonia or respiratory distress
2. Encephalopathy
3. Acute onset neuromuscular symptoms
4. Otherwise unexplained rash with fever
5. Fever with mucous membrane bleeding
6. Unexplained acute icteric sydromes
7. Massive diarrhea with dehydration and collapse

In the setting of any of the following:

1. Atypical host characteristics:
   - Young (< 50 years)
   - Immunologically intact
   - No underlying illness
   - No recent international travel or other exposure to potential source of infection

2. Serious, unexpected, acute illness
   - Abrupt onset
   - Prostration
   - Cardiovascular collapse
   - Respiratory distress
   - Obtundation/change in mental status
   - Disseminated intravascular coagulation

3. Multiple similarly presenting cases, especially if
   - Geographically associated, or
   - Closely clustered in time

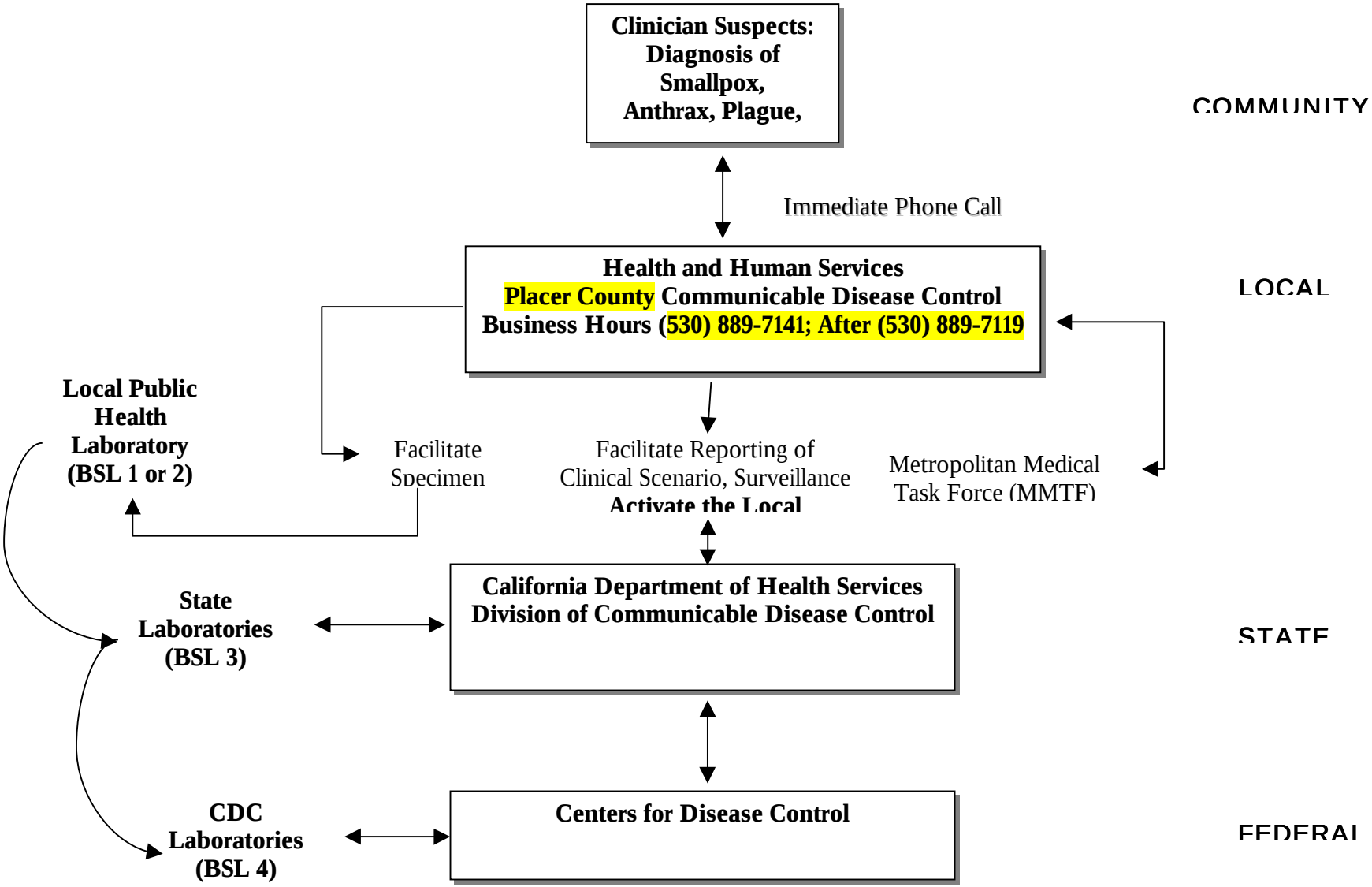
4. Increases in common syndromes occurring out of season
   - Influenza-like-illness in the summer

Please call the Placer County Health and Human Services, Communicable Disease Control <u>immediately</u>. We would like to hear from you even if you only have <u>some</u> suspicion that something isn't quite right.

During business hours (M-F, 8 am – 5 pm)	**(530) 889-7141**
After hours, call county communications and ask to speak with the Health Officer or Disease Control Officer	**(530) 889-7119**
Public Health Laboratory (specimen submission, routing info)	**(530) 889-7205**

REVISED 10/19/01

Reporting Suspected Bioterrorism Related Illness



DISEASE REPORTING

PLACER COUNTY HEALTH AND HUMAN SERVICES COMMUNICABLE DISEASE CONTROL

Physicians and health care providers must report the following conditions.
Suspected, lab-confirmed, and/or clinical diagnoses are reportable within specified time intervals.
Reporting enables appropriate public health interventions.

PHONE
(530) 889-7141 or after 5:00 P.M.
(530) 889-7119
IMMEDIATELY:

- Anthrax
- Botulism
- Cholera
- Dengue
- Diptheria
- E-coli O157 infection
- Hantavirus infections
- Hemolytic Uremic Syndrome
- Measles
- Meningococcal infections
- Plague (any form)
- Rabies (any form)
- Seafood poisoning
  - Domoic Acid
  - Ciguatera
  - Scrombroid
  - Paralytic Shellfish
- Viral Hemorrhagic Fevers
- Yellow Fever
- Outbreaks
  - Neonatal diarrhea

PHONE (530) 889-7141 0R
FAX (530) 889-7198
ONE WORKING DAY:

- Amebiasis
- Anisakiasis
- Babesiosis
- Campylobacteriosis
- Colorado Tick Fever
- Cryptosporidiosis
- Encephalitis (infectious)
- Ehrlichiosis
- *Haemophilus influenzae* (invasive)
- Hepatitis A
- Listeriosis
- Lymphocytic choriomeningitis
- Malaria
- Meningitis
- Neonatal conjunctivitis
- Pertussis

Any food- or water-borne illness

- Psittacosis
- Poliomyelitis
- Q Fever
- Relapsing Fever
- RMSF
- Salmonellosis
- Shigellosis
- Streptococcal Infections
  - Food handlers and Dairy workers only
- Syphilis
- Swimmer's itch
- Trichinosis
- Typhoid
- Typus Fever
- Tuberculosis
- *Vibrio* infections
- Yersiniosis

PHONE, FAX, OR MAIL WITHIN ONE WEEK:

- AIDS
- Aspergillosis
- Brucellosis
- Chancroid
- Chlamydial infections
- Coccidioidomycosis
- Cysticercosis
- Echinococcosis
- Giardiasis
- Gonococcal infections
- Hepatitis B,C,D
- Hepatitis, other viral
- Kawasaki's syndrome
- Legionellosis
- Leprosy
- Leptospirosis
- Lyme Disease
- MRSA
- Mumps
- NGU
- PID
- Reye's syndrome
- Rheumatic fever, acute
- Rubella
- infections/sndrome
- Tetanus
- Toxic shock syndrome
- Toxoplasmosis
- Tuleremia
- VRE

Monday – Friday 8 AM to 5 PM, call:
Placer County Health and Human Services, Communicable Disease Control
11484 B Avenue, Auburn, California 95603 (530) 889-7141 FAX (530)-889-7198

Last Revised 10/19/01

Selected Biowarfare Agent Characteristics

Disease		Person-to-Person transmission	Infective Dose (Aerosol)	Incubation Period	Duration of Illness	Lethality	Persistance of Organism	Treatment
Inhalation anthrax	Fever, malaise, cough, respiratory distress	No	8,000-50,000 spores	1-6 days	3-5 days (usually fatal if untreated)	High	spores remain viable in soil for > 40 yrs	Ciprofloxacin Doxycycline
Pneumonic Plague	High fever, chills, headache, productive cough – watery then bloody	High	<100 organisms	2-3 days	1-6 days (usually fatal)	High unless treated within 12-24 hours	For up to 1 year in soil; 270 days in live tissue	Streptomycin Gentamycin or Chloramphenicol
Botulism	Dry throat, blurred vision, slurred speech, difficulty swallowing, progressive descending symmetrical paralysis	No	0.001 μg/kg is LD_{50} for type A	12-36 hours (range up to several days)	Death in 24-72 hours; lasts months if not lethal	High without respiratory support	For weeks in non-moving water and food	Antitoxin Supportive care
Smallpox	Non-specific flu-like prodrome (malaise, fever, headache) then synchronously evolving maculopapular rash progressing to vesicles then pustules	High	Assumed low (10-100 organisms)	12-14 days (range 7-17 days)	4 weeks	High to moderate	Very stable	?Cidofovir
Brucellosis	Irregular fever, chills, headache, malaise, cough and chest pain in 20%, osteoarticular disease	No	10–100 organisms	5-60 days (average 1-2 months)	Weeks to months	≤5% untreated	6 weeks in dust and 10 weeks in soil or water	Doxycycline + Rifampin
Tularemia	Fever, headache, malaise, weight loss, nonproductive cough	No	10-50 organisms	3-6 days (range 1-21 days)	≥ 2 weeks	Moderate if untreated	For months in moist soil or other media	Streptomycin Gentamycin
Q Fever	Fever, chills, headache, diaphoresis, malaise, fatigue, anorexia, and weight loss	Rare	1-10 organisms	7 days (range 2-14 days)	Weeks	Very low	Able to withstand heat and drying; persists in environment for weeks to months	Tetracycline Doxycycline
Viral Encephalitdes	Fever, rigors, severe headache, photophobia, malaise, nausea, vomiting, diarrhea may follow	Low	10-100 organisms	1-5 days	Days to weeks	Variable	Relatively unstable in the environment	Supportive care
Viral Hemorrhagic Fevers	Fever, malaise, myalgia, prostration; vascular permeability may present as conjunctival injection and petechial hemmorage and progress to mucous membrane hemmorhage and shock	Moderate	1-10 organisms	4-21 days	Days to weeks	5 – 90 % case fatality rate depending on virus	Relatively unstable in the environment	Ribavirin Supportive care
Staph Enterotoxin B	Sudden onset fever, chills, headache, myalgias, non-productive cough	No	30 ng/person incapacitation	3-12 hours after inhalation	Days	<1%	Resistant to freezing	Supportive care
Ricin	Depends on route of exposure. Aerosol route: fever, chest tightness, cough, hypothermia. Oral route: gastrointestinal hemmorhage	No	3-5μg/kg is LD_{50}	18-24 hours	Days. Death within 10-12 days for ingestion	High	Stable	Inhalation: supportive GI: lavage, charcoal, cathartics
T-2 Mycotoxins	Skin pain, redness, necrosis, sloughing of epidermis, wheezing, chest pain, hemoptysis	No	Moderate	Minutes to hours	Variable. Death may occur in min., hrs. or days	Moderate	For years at room temperature	Supportive care

LD_{50} = Lethal Dose μg/kg
Ricin and botulinum are lethal at all levels.
? = may be effective

Source: Adapted from Medical Management of Biological Casualties – USAMRID 1998

Last Revised 10/19/01

SMALLPOX

ALL SUSPECT CASES OF SMALLPOX MUST BE REPORTED IMMEDIATELY TO THE HEALTH AND HUMAN SERVICES COMMUNICABLE DISEASE CONTROL:

During business hours: (530) 889-7141
After hours (Health Officer Richard J. Burton, M.D., M.P.H.): (530) 889-7119

(In the event that you are unable to reach a Communicable Disease Control Contact, please call the Placer County Office of Emergency Services at (530) 886-5300 during business hours, or 24-hour dispatch at (530) 886-5375 after business hours.)

Epidemiology:

- Highly infectious after aerosolization
- Person-to-person transmission can occur via droplet nuclei or aerosols expelled from the oropharynx and by direct contact
- Contaminated clothing or bed linens can also spread the virus
- About 30% of susceptible contacts will become infected

Clinical:

- Incubation period is 12-14 days (ranges 7-17 days)
- Characteristic rash appears 2-3 days after nonspecific, flu-like prodrome (fever and headache)
- Maculopapular rash begins on mucosa of mouth and pharynx, face, hands, forearms and spreads to legs and centrally to trunk; lesions are more predominant on the face and extremities than on the trunk.
- Lesions progress synchronously on any given part of the body from macules to papules to vesicles to pustules to crusty scabs

Laboratory Diagnosis:

- Mask and gloves should be worn by person obtaining specimen, preferably a person who has been recently vaccinated
- Vesicular fluid is obtained by opening lesions with the blunt edge of a scalpel, harvesting fluid with a cotton swab; scabs can be removed by forceps. Swabs and scabs should be placed in a vacutainer, sealed with tape, and placed in a second, durable, watertight container
- Laboratory specimens must be handled in a Biosafety Level 4 facility (e.g. CDC) and will be evaluated with electron microscopy and cell culture
- Contact the Placer County Public Health Laboratory for assistance.

Patient Isolation:

- Strict isolation in negative pressure room (high efficiency particulate air filtration ideal) from onset of rash until all scabs separate
- Laundry and waste should be autoclaved before being laundered or incinerated

Treatment:

- Supportive care is the mainstay of therapy
- In-vitro antiviral activity against poxviruses has been shown with adefovir, cidofovir, dipivoxil, and ribavirin. (Animal studies suggest that cidofovir may be most effective).

Prophylaxis:

- Smallpox vaccine would be required for all persons exposed at the time of the bioterrorist attack or anyone with close personal contact with a smallpox case
- Vaccine is most effective if given before of within 3 days of exposure
- Ideally, all exposed persons should be placed in strict quarantine for 17 days after last contact with a smallpox case

Smallpox as a Biological Weapon
Medical and Public Health Management

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Jerome Hauer, MPH
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Kevin Tonat, PhD
for the Working Group on Civilian Biodefense

Objective To develop consensus-based recommendations for measures to be taken by medical and public health professionals following the use of smallpox as a biological weapon against a civilian population.

Participants The working group included 21 representatives from staff of major medical centers and research, government, military, public health, and emergency management institutions and agencies.

Evidence The first author (D.A.H.) conducted a literature search in conjunction with the preparation of another publication on smallpox as well as this article. The literature identified was reviewed and opinions were sought from experts in the diagnosis and management of smallpox, including members of the working group.

Consensus Process The first draft of the consensus statement was a synthesis of information obtained in the evidence-gathering process. Members of the working group provided formal written comments that were incorporated into the second draft of the statement. The working group reviewed the second draft on October 30, 1998. No significant disagreements existed and comments were incorporated into a third draft. The fourth and final statement incorporates all relevant evidence obtained by the literature search in conjunction with final consensus recommendations supported by all working group members.

Conclusions Specific recommendations are made regarding smallpox vaccination, therapy, postexposure isolation and infection control, hospital epidemiology and infection control, home care, decontamination of the environment, and additional research needs. In the event of an actual release of smallpox and subsequent epidemic, early detection, isolation of infected individuals, surveillance of contacts, and a focused selective vaccination program will be the essential items of an effective control program.

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THIS IS THE SECOND ARTICLE IN a series entitled *Medical and Public Health Management Following the Use of a Biological Weapon: Consensus Statements of the Working Group on Civilian Biodefense*.[1] The working group has identified a limited number of widely known organisms that could cause disease and deaths in sufficient numbers to cripple a city or region. Smallpox is one of the most serious of these diseases.

If used as a biological weapon, smallpox represents a serious threat to civilian populations because of its case-fatality rate of 30% or more among unvaccinated persons and the absence of specific therapy. Although smallpox has long been feared as the most devastating of all infectious diseases,[2] its potential for devastation today is far greater than at any previous time. Routine vaccination throughout the United States ceased more than 25 years ago. In a now highly susceptible, mobile population, smallpox would be able to spread widely and rapidly throughout this country and the world.

CONSENSUS METHODS

Members of the working group were selected by the chairman in consultation with principal agency heads in the Department of Health and Human Services (DHHS) and the US Army Medical Research Institute of Infectious Diseases (USAMRIID).

The first author (D.A.H.) conducted a literature search in conjunction with the preparation of another

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publication on smallpox[2] as well as this article. The literature was reviewed and opinions were sought from experts in the diagnosis and management of smallpox, including members of the working group.

The first draft of the working group's consensus statement was the result of synthesis of information obtained in the evidence-gathering process. Members of the working group were asked to make written comments on the first draft of the document in September 1998. Suggested revisions were incorporated into the second draft of the statement. The working group was convened to review the second draft of the statement on October 30, 1998. Consensus recommendations were made and no significant disagreements existed at the conclusion of this meeting. The third draft incorporated changes suggested at the conference and working group members had an additional opportunity to suggest final revisions. The final statement incorporates all relevant evidence obtained by the literature search in conjunction with final consensus recommendations supported by all working group members.

This article is intended to provide the scientific foundation and initial framework for the detailed planning that would follow a bioterrorist attack with smallpox. This planning must encompass coordinated systems approaches to bioterrorism, including public policies and consequence management by local and regional public and private institutions. The assessment and recommendations provided herein represent the best professional judgment of the working group at this time based on data and expertise currently available. The conclusions and recommendations need to be regularly reassessed as new information becomes available.

HISTORY AND POTENTIAL AS A BIOWEAPON

Smallpox probably was first used as a biological weapon during the French and Indian Wars (1754-1767) by British forces in North America.[3] Soldiers distributed blankets that had been used by smallpox patients with the intent of initiating outbreaks among American Indians. Epidemics occurred, killing more than 50% of many affected tribes. With Edward Jenner's demonstration in 1796 that an infection caused by cowpox protected against smallpox and the rapid diffusion worldwide of the practice of cowpox inoculation (ie, vaccination),[4] the potential threat of smallpox as a bioweapon was greatly diminished.

A global campaign, begun in 1967 under the aegis of the World Health Organization (WHO), succeeded in eradicating smallpox in 1977.[1] In 1980, the World Health Assembly recommended that all countries cease vaccination.[5] A WHO expert committee recommended that all laboratories destroy their stocks of variola virus or transfer them to 1 of 2 WHO reference laboratories—the Institute of Virus Preparations in Moscow, Russia, or the Centers for Disease Control and Prevention (CDC) in Atlanta, Ga. All countries reported compliance. The WHO committee later recommended that all virus stocks be destroyed in June 1999, and the 1996 World Health Assembly concurred.[6] In 1998, possible research uses for variola virus were reviewed by a committee of the Institute of Medicine (IOM).[7] The IOM committee concluded, as did the preceding WHO committee, that there were research questions that might be addressed if the virus were to be retained. However, the IOM committee did not explore the costs or relative priority to be assigned to such an effort, and that committee was not asked to weigh the possible benefits resulting from such research activities contrasted with the possible benefits resulting from an international decision to destroy all virus stocks. These considerations will be weighed and decided by the 1999 World Health Assembly.

Recent allegations from Ken Alibek, a former deputy director of the Soviet Union's civilian bioweapons program, have heightened concern that smallpox might be used as a bioweapon. Alibek[8] reported that beginning in 1980, the Soviet government embarked on a successful program to produce the smallpox virus in large quantities and adapt it for use in bombs and intercontinental ballistic missiles; the program had an industrial capacity capable of producing many tons of smallpox virus annually. Furthermore, Alibek reports that Russia even now has a research program that seeks to produce more virulent and contagious recombinant strains. Because financial support for laboratories in Russia has sharply declined in recent years, there are increasing concerns that existing expertise and equipment might fall into non-Russian hands.

The deliberate reintroduction of smallpox as an epidemic disease would be an international crime of unprecedented proportions, but it is now regarded as a possibility. An aerosol release of variola virus would disseminate widely, given the considerable stability of the orthopoxviruses in aerosol form[9] and the likelihood that the infectious dose is very small.[10] Moreover, during the 1960s and 1970s in Europe, when smallpox was imported during the December to April period of high transmission, as many as 10 to 20 second-generation cases were often infected from a single case. Widespread concern and, sometimes, panic occurred, even with outbreaks of fewer than 100 cases, resulting in extensive emergency control measures.[2]

EPIDEMIOLOGY

Smallpox was once worldwide in scope, and before vaccination was practiced, almost everyone eventually contracted the disease. There were 2 principal forms of the disease, variola major and a much milder form, variola minor (or alastrim). Before eradication took place, these forms could be differentiated clinically only when occurring in outbreaks; virological differentiation is now possible.[11,12] Through the end of the 19th century, variola major predominated throughout the world. However, at the turn of the century, variola minor was first detected in South Africa and later in Florida, from whence it spread

across the United States and into Latin America and Europe.[13] Typical variola major epidemics such as those that occurred in Asia resulted in case-fatality rates of 30% or higher among the unvaccinated, whereas variola minor case-fatality rates were customarily 1% or less.[2]

Smallpox spreads from person to person,[10,14] primarily by droplet nuclei or aerosols expelled from the oropharynx of infected persons and by direct contact. Contaminated clothing or bed linens can also spread the virus.[15] There are no known animal or insect reservoirs or vectors.

Historically, the rapidity of smallpox transmission throughout the population was generally slower than for such diseases as measles or chickenpox. Patients spread smallpox primarily to household members and friends; large outbreaks in schools, for example, were uncommon. This finding was accounted for in part by the fact that transmission of smallpox virus did not occur until onset of rash. By then, many patients had been confined to bed because of the high fever and malaise of the prodromal illness. Secondary cases were thus usually restricted to those who came into contact with patients, usually in the household or hospital.

The seasonal occurrence of smallpox was similar to that of chickenpox and measles—its incidence was highest during winter and early spring.[16] This pattern was consonant with the observation that the duration of survival of orthopoxviruses in the aerosolized form was inversely proportional to both temperature and humidity.[9] Likewise, when imported cases occurred in Europe, large outbreaks sometimes developed during the winter months, rarely during the summer.[17]

The patient was most infectious from onset of rash through the first 7 to 10 days of rash (FIGURE 1).[17,18] As scabs formed, infectivity waned rapidly. Although the scabs contained large amounts of viable virus, epidemiological and laboratory studies indicate that they were not especially infectious, presumably because the virions were bound tightly in the fibrin matrix.[19]

The age distribution of cases depended primarily on the degree of smallpox susceptibility in the population. In most areas, cases predominated among children because adults were protected by immunity induced by vaccination or previous smallpox infection. In rural areas that had seen little vaccination or smallpox, the age distribution of cases was similar to the age distribution of the population. The age distribution pattern of cases in the United States presumably would be such if smallpox were to occur now because vaccination immunity in the population has waned so substantially.

MICROBIOLOGY

Smallpox, a DNA virus, is a member of the genus orthopoxvirus.[20] The orthopoxviruses are among the largest and most complex of all viruses. The virion is characteristically a brick-shaped structure with a diameter of about 200 nm. Three other members of this genus (monkeypox, vaccinia, and cowpox) can also infect humans, causing cutaneous lesions, but only smallpox is readily transmitted from person to person.[2] Monkeypox, a zoonotic disease, presently is found only in tropical rain forest areas of central and western Africa and is not readily transmitted among humans.[21] Vaccinia and cowpox seldom spread from person to person.

PATHOGENESIS AND CLINICAL PRESENTATION

Natural infection occurs following implantation of the virus on the oropharyngeal or respiratory mucosa.[2] The infectious dose is unknown but is believed to be only a few virions.[10] After the migration of virus to and multiplication in regional lymph nodes, an asymptomatic viremia develops on about the third or fourth day, followed by multiplication of virus in the spleen, bone marrow, and lymph nodes. A secondary viremia begins on about the eighth day and is followed by fever and toxemia. The virus, contained in leukocytes, then localizes in small blood vessels of the dermis and beneath the oral and pharyngeal mucosa and subsequently infects adjacent cells.

At the end of the 12- to 14-day incubation period (range, 7-17 days), the patient typically experiences high fever, malaise, and prostration with headache and backache.[2] Severe abdominal pain and delirium are sometimes present. A maculopapular rash then appears on the mucosa of the mouth and pharynx, face, and forearms, and spreads to the trunk and legs (FIGURE 2).[2] Within 1 to 2 days, the rash becomes vesicular and, later, pustu-

Figure 1. Typical Temperature Chart of Patient With Smallpox Infection

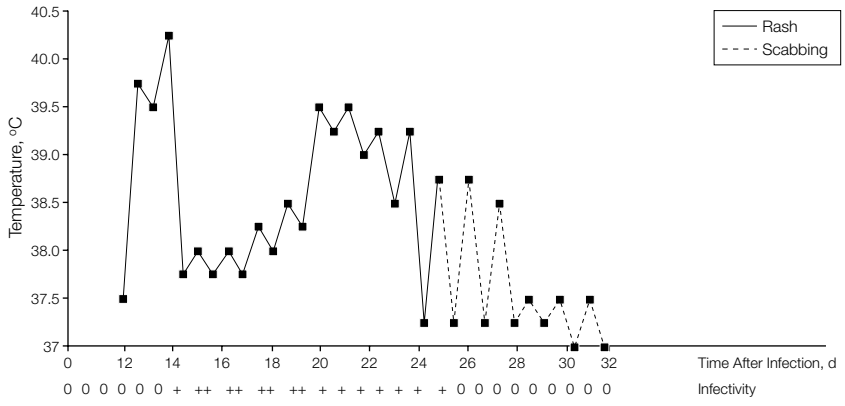


Chart shows approximate time of appearance, evolution of the rash, and magnitude of infectivity relative to the number of days after acquisition of infection.[3,26,29]

lar. The pustules are characteristically round, tense, and deeply embedded in the dermis; crusts begin to form on about the eighth or ninth day of rash. As the patient recovers, the scabs separate and characteristic pitted scarring gradually develops. The scars are most evident on the face and result from the destruction of sebaceous glands followed by shrinking of granulation tissue and fibrosis.[2]

The lesions that first appear in the mouth and pharynx ulcerate quickly because of the absence of a stratum corneum, releasing large amounts of virus into the saliva.[22] Virus titers in saliva are highest during the first week of illness, corresponding with the period during which patients are most infectious. Although the virus in some instances can be detected in swabs taken from the oropharynx as many as 5 to 6 days before the rash develops,[22] transmission does not occur during this period.

Except for the lesions in the skin and mucous membranes and reticulum cell hyperplasia, other organs are seldom involved. Secondary bacterial infection is not common, and death, which usually occurs during the second week of illness, most likely results from the toxemia associated with circulating immune complexes and soluble variola antigens.[2] Encephalitis sometimes ensues that is indistinguishable from the acute perivascular demyelination observed as a complication of infection due to vaccinia, measles, or varicella.[23]

Neutralizing antibodies can be detected by the sixth day of rash and remain at high titers for many years.[24] Hemagglutinin-inhibiting antibodies can be detected on about the sixth day of rash, or about 21 days after infection, and complement-fixing antibodies appear approximately 2 days later. Within 5 years, hemagglutinin-inhibiting antibodies decline to low levels and complement-fixing antibodies rarely persist for longer than 6 months.[2]

Although at least 90% of smallpox cases are clinically characteristic and readily diagnosed in endemic areas, 2 other forms of smallpox are difficult to recognize—hemorrhagic and malignant. Hemorrhagic cases are uniformly fatal and occur among all ages and in both sexes, but pregnant women appear to be unusually susceptible. Illness usually begins with a somewhat shorter incubation period and is characterized by a severely prostrating prodromal illness with high fever and head, back, and abdominal pain. Soon thereafter, a dusky erythema develops, followed by petechiae and frank hemorrhages into the skin and mucous membranes. Death usually occurs by the fifth or sixth day after onset of rash.[23]

In the frequently fatal malignant form, the abrupt onset and prostrating constitutional symptoms are similar. The confluent lesions develop slowly, never progressing to the pustular stage but remaining soft, flattened, and velvety to the touch. The skin has the appearance of a fine-grained, reddish-colored crepe rubber, sometimes with hemorrhages. If the patient survives, the lesions gradually disappear without forming scabs or, in severe cases, large amounts of epidermis might peel away.[23]

The illness associated with variola minor is generally less severe, with fewer constitutional symptoms and a more sparse rash.[25] A milder form of disease is also seen among those who have residual immunity from previous vaccination. In partially immune persons, the rash tends to be atypical and more scant and the evolution of the lesions more rapid.[15]

There is little information about how individuals with different types of immune deficiency responded to natural smallpox infection. Smallpox was eradicated before human immunodeficiency virus (HIV) was identified and

Figure 2. Typical Case of Smallpox Infection in a Child

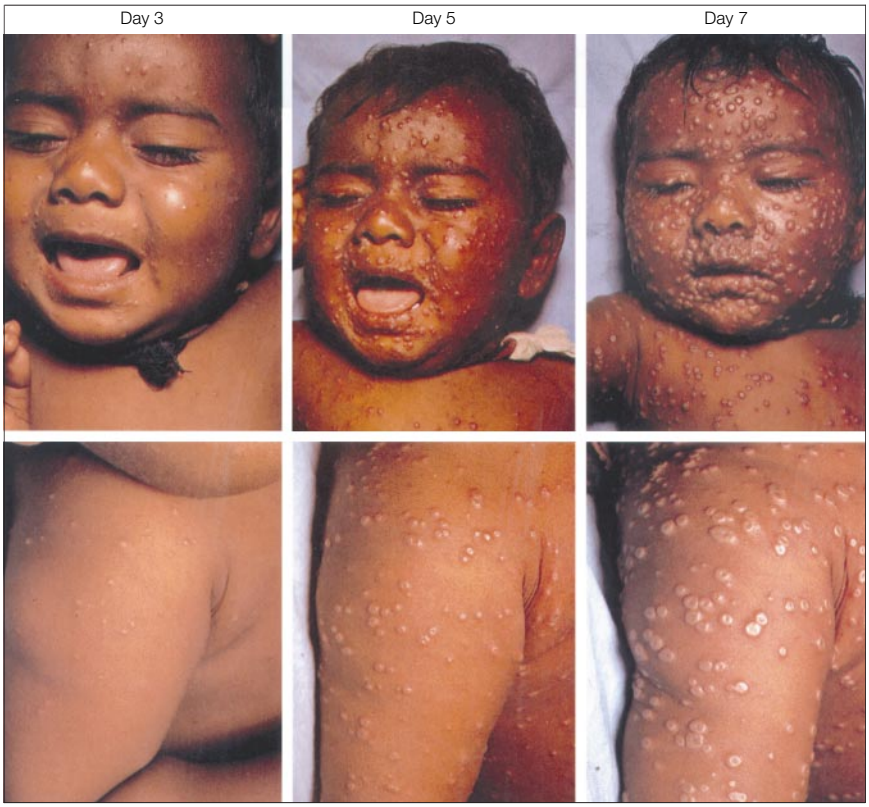


Figure shows the appearance of the rash at days 3, 5, and 7 of evolution. Note that lesions are more dense on the face and extremities than on the trunk; that they appear on the palms of the hand; and that they are similar in appearance to each other. If this were a case of chickenpox, one would expect to see, in any area, macules, papules, pustules, and lesions with scabs. Reproduced with permission from the World Health Organization.[2]

before suitable techniques became available for measuring cell-mediated immunity. However, it is probable that the underlying cause of some cases of malignant and hemorrhagic smallpox resulted from defective immune responses. Vaccination of immune-deficient persons sometimes resulted in a continually spreading primary lesion, persistent viremia, and secondary viral infection of many organs. One such case is documented to have occurred in a vaccinated soldier who had HIV infection.[26]

DIAGNOSIS

The discovery of a single suspected case of smallpox must be treated as an international health emergency and be brought immediately to the attention of national officials through local and state health authorities.

The majority of smallpox cases present with a characteristic rash that is centrifugal in distribution, ie, most dense on the face and extremities. The lesions appear during a 1- to 2-day period and evolve at the same rate. On any given part of the body, they are generally at the same stage of development. In varicella (chickenpox), the disease most frequently confused with smallpox, new lesions appear in crops every few days and lesions at very different stages of maturation (ie, vesicles, pustules, and scabs) are found in adjacent areas of skin. Varicella lesions are much more superficial and are almost never found on the palms and soles. The distribution of varicella lesions is centripetal, with a greater concentration of lesions on the trunk than on the face and extremities.

The signs and symptoms of both hemorrhagic and malignant smallpox were such that smallpox was seldom suspected until more typical cases were seen and it was recognized that a smallpox outbreak was in progress. Hemorrhagic cases were most often initially identified as meningococcemia or severe acute leukemia. Malignant cases likewise posed diagnostic problems, most often being mistaken for hemorrhagic chickenpox or prompting surgery because of severe abdominal pain.

Laboratory confirmation of the diagnosis in a smallpox outbreak is important. Specimens should be collected by someone who has recently been vaccinated (or is vaccinated that day) and who wears gloves and a mask. To obtain vesicular or pustular fluid, it is often necessary to open lesions with the blunt edge of a scalpel. The fluid can then be harvested on a cotton swab. Scabs can be picked off with forceps. Specimens should be deposited in a vacutainer tube that should be sealed with adhesive tape at the juncture of stopper and tube. This tube, in turn, should be enclosed in a second durable, watertight container. State or local health department laboratories should immediately be contacted regarding the shipping of specimens. Laboratory examination requires high-containment (BL-4) facilities and should be undertaken only in designated laboratories with the appropriate training and equipment. Once it is established that the epidemic is caused by smallpox virus, clinically typical cases would not require further laboratory confirmation.

Smallpox infection can be rapidly confirmed in the laboratory by electron microscopic examination of vesicular or pustular fluid or scabs. Although all orthopoxviruses exhibit identically appearing brick-shaped virions, history taking and clinical picture readily identify cowpox and vaccinia. Although smallpox and monkeypox virions may be indistinguishable, naturally occurring monkeypox is found only in tropical rain forest areas of Africa. Definitive laboratory identification and characterization of the virus involves growth of the virus in cell culture or on chorioallantoic egg membrane and characterization of strains by use of various biologic assays, including polymerase chain reaction techniques and restriction fragment-length polymorphisms.[27-29] The latter studies can be completed within a few hours.

PREEXPOSURE PREVENTIVE VACCINATION

Before 1972, smallpox vaccination was recommended for all US children at age 1 year. Most states required that each child be vaccinated before school entry. The only other requirement for vaccination was for military recruits and tourists visiting foreign countries. Most countries required that the individual be successfully vaccinated within a 3-year period prior to entering the country. Routine vaccination in the United States stopped in 1972 and since then, few persons younger than 27 years have been vaccinated. The US Census Bureau reported that in 1998, approximately 114 million persons, or 42% of the US population, were aged 29 years or younger.[30]

In addition, the immune status of those who were vaccinated more than 27 years ago is not clear. The duration of immunity, based on the experience of naturally exposed susceptible persons, has never been satisfactorily measured. Neutralizing antibodies are reported to reflect levels of protection, although this has not been validated in the field. These antibodies have been shown to decline substantially during a 5- to 10-year period.[24] Thus, even those who received the recommended single-dose vaccination as children do not have lifelong immunity. However, among a group who had been vaccinated at birth and at ages 8 and 18 years as part of a study, neutralizing antibody levels remained stable during a 30-year period.[31] Because comparatively few persons today have been successfully vaccinated on more than 1 occasion, it must be assumed that the population at large is highly susceptible to infection.

In the United States, a limited reserve supply of vaccine that was produced by Wyeth Laboratories, Lancaster, Pa, in the 1970s is in storage. This supply is believed to be sufficient to vaccinate between 6 and 7 million persons. This vaccine, now under the control of the CDC, consists of vaccine virus (New York Board of Health strain) grown on scarified calves. After purification, it was freeze-dried in rubber-stoppered vials that contain sufficient vaccine for at least 50 doses when a bifurcated needle is used. It is stored at –20°C (James LeDuc, PhD, oral communication, 1998). Although quantities of vaccine have also been retained

by a number of other countries, none have reserves large enough to meet more than their own potential emergency needs. WHO has 500 000 doses.[32]

There are no manufacturers now equipped to produce smallpox vaccine in large quantities. The development and licensure of a tissue cell culture vaccine and the establishment of a new vaccine production facility is estimated to require at least 36 months (Thomas Monath, MD, unpublished data, 1999).

Because of the small amounts of vaccine available, a preventive vaccination program to protect individuals such as emergency and health care personnel is not an option at this time. When additional supplies of vaccine are procured, a decision to undertake preventive vaccination of some portion of the population will have to weigh the relative risk of vaccination complications against the threat of contracting smallpox.

A further deterrent to extensive vaccination is the fact that presently available supplies of vaccinia immune globulin (VIG), also maintained by the CDC, are very limited in quantity. The working group recommends VIG for the treatment of severe cutaneous reactions occurring as a complication of vaccination.[33,34] Vaccinia immune globulin has also been given along with vaccination to protect those who needed vaccination but who were at risk of experiencing vaccine-related complications.[33] It has been estimated that if 1 million persons were vaccinated, as many as 250 persons would experience adverse reactions of a type that would require administration of VIG (James LeDuc, PhD, oral communication, 1998). How much VIG would be needed to administer with vaccine to those at risk is unknown.

POSTEXPOSURE THERAPY

At this time, the best that can be offered to the patient infected with smallpox is supportive therapy plus antibiotics as indicated for treatment of occasional secondary bacterial infections. No antiviral substances have yet proved effective for the treatment of smallpox, and the working group is not aware of any reports that suggest any antiviral product is therapeutic. Encouraging initial reports in the 1960s describing the therapeutic benefits of the thiosemicarbazones, cytosine arabinoside, and adenine arabinoside proved questionable on further study.[21,35,36]

Recent studies on tissue culture, mice, and a small number of monkeys have suggested the possibility that cidofovir, a nucleoside analog DNA polymerase inhibitor, might prove useful in preventing smallpox infection if administered within 1 or 2 days after exposure (John Huggins, PhD, oral communication, 1998). At this time, there is no evidence that cidofovir is more effective than vaccination in this early period. Moreover, the potential utility of this drug is limited, given the fact that it must be administered intravenously and its use is often accompanied by serious renal toxicity.[37]

POSTEXPOSURE INFECTION CONTROL

A smallpox outbreak poses difficult public health problems because of the ability of the virus to continue to spread throughout the population unless checked by vaccination and/or isolation of patients and their close contacts.

A clandestine aerosol release of smallpox, even if it infected only 50 to 100 persons to produce the first generation of cases, would rapidly spread in a now highly susceptible population, expanding by a factor of 10 to 20 times or more with each generation of cases.[2,10,38] Between the time of an aerosol release of smallpox virus and diagnosis of the first cases, an interval as long as 2 weeks or more is apt to occur because of the average incubation period of 12 to 14 days and the lapse of several additional days before a rash was sufficiently distinct to suggest the diagnosis of smallpox. By that time, there would be no risk of further environmental exposure from the original aerosol release because the virus is fully inactivated within 2 days.

As soon as the diagnosis of smallpox is made, all individuals in whom smallpox is suspected should be isolated immediately and all household and other face-to-face contacts should be vaccinated and placed under surveillance. Because the widespread dissemination of smallpox virus by aerosol poses a serious threat in hospitals, patients should be isolated in the home or other nonhospital facility whenever possible. Home care for most patients is a reasonable approach, given the fact that little can be done for a patient other than to offer supportive therapy.

In the event of an aerosol release of smallpox and a subsequent outbreak, the rationale for vaccinating patients suspected to have smallpox at this time is to ensure that some with a mistaken diagnosis are not placed at risk of acquiring smallpox. Vaccination administered within the first few days after exposure and perhaps as late as 4 days may prevent or significantly ameliorate subsequent illness.[39] An emergency vaccination program is also indicated that would include all health care workers at clinics or hospitals that might receive patients; all other essential disaster response personnel, such as police, firefighters, transit workers, public health staff, and emergency management staff; and mortuary staff who might have to handle bodies. The working group recommends that all such personnel for whom vaccination is not contraindicated should be vaccinated immediately irrespective of prior vaccination status.

Vaccination administered within 4 days of first exposure has been shown to offer some protection against acquiring infection and significant protection against a fatal outcome.[15] Those who have been vaccinated at some time in the past will normally exhibit an accelerated immune response. Thus, it would be prudent, when possible, to assign those who had been previously vaccinated to duties involving close patient contact.

It is important that discretion be used in identifying contacts of patients to ensure, to the extent that is possible, that vaccination and adequate surveillance measures are focused on those at great-

est risk. Specifically, it is recommended that *contacts* be defined as persons who have been in the same household as the infected individual or who have been in face-to-face contact with the patient after the onset of fever. Experience during the smallpox global eradication program showed that patients did not transmit infection until after the prodromal fever had given way to the rash stage of illness.[17,18]

Isolation of all contacts of exposed patients would be logistically difficult and, in practice, should not be necessary. Because contacts, even if infected, are not contagious until onset of rash, a practical strategy calls for all contacts to have temperatures checked at least once each day, preferably in the evening. Any increase in temperature higher than 38°C (101°F) during the 17-day period following last exposure to the case would suggest the possible development of smallpox[2] and be cause for isolating the patient immediately, preferably at home, until it could be determined clinically and/or by laboratory examination whether the contact had smallpox. All close contacts of the patients should be promptly vaccinated.

Although cooperation by most patients and contacts in observing isolation could be ensured through counseling and persuasion, there may be some for whom forcible quarantine will be required. Some states and cities in the United States, but not all, confer broad discretionary powers on health authorities to ensure the safety of the public's health and, at one time, this included powers to quarantine. Under epidemic circumstances, this could be an important power to have. Thus, each state and city should review its statutes as part of its preparedness activities.

During the smallpox epidemics in the 1960s and 1970s in Europe, there was considerable public alarm whenever outbreaks occurred and, often, a demand for mass vaccination throughout a very widespread area, even when the vaccination coverage of the population was high.[2] In the United States, where few people now have protective levels of immunity, such levels of concern must be anticipated. However, the US vaccine supply is limited at present; thus, vaccine would have to be carefully conserved and used in conjunction with measures to implement rapid isolation of smallpox patients.

HOSPITAL EPIDEMIOLOGY AND INFECTION CONTROL

Smallpox transmission within hospitals has long been recognized as a serious problem. For this reason, separate hospitals for smallpox patients were used for more than 200 years. Throughout the 1970s, both England and Germany had fully equipped standby hospitals in case smallpox should be imported.[2] Infections acquired in hospitals may occur as the result of droplets spread from patients to staff and visitors in reasonably close contact or by a fine particle aerosol. In 1 such occurrence in Germany, a smallpox patient with a cough, although isolated in a single room, infected persons on 3 floors of a hospital.[10] Persons with the usually fatal hemorrhagic or malignant forms of the disease pose a special problem because they often remain undiagnosed until they are near death and extremely contagious. A number of outbreaks have occurred in laundry workers who handled linens and blankets used by patients.[15] The working group recommends that in an outbreak setting, all hospital employees as well as patients in the hospital be vaccinated. For individuals who are immunocompromised or for whom vaccination is otherwise contraindicated, VIG should be provided, if available. If it is not available, a judgment will have to be made regarding the relative risks of acquiring the disease in contrast with the risks associated with vaccination.

In the event of a limited outbreak with few cases, patients should be admitted to the hospital and confined to rooms that are under negative pressure and equipped with high-efficiency particulate air filtration. In larger outbreaks, home isolation and care should be the objective for most patients. However, not all will be able to be so accommodated and, to limit nosocomial infections, authorities should consider the possibility of designating a specific hospital or hospitals for smallpox care. All persons isolated as such and those caring for them should be immediately vaccinated. Employees for whom vaccination is contraindicated should be furloughed.

Standard precautions using gloves, gowns, and masks should be observed. All laundry and waste should be placed in biohazard bags and autoclaved before being laundered or incinerated. A special protocol should be developed for decontaminating rooms after they are vacated by patients (see "Decontamination" section).

Laboratory examination requires high-containment (BL-4) facilities and should be undertaken only in designated laboratories with the appropriate trained personnel and equipment. Specific recommendations for safe specimen transport are described in the section on "Differential Diagnosis and Diagnostic Tests."

Protecting against the explosive spread of virus from the hemorrhagic or malignant case is difficult. Such cases occurring during the course of an outbreak may be detected if staff is alert to the possibility that any severe, acute, prostrating illness must be considered smallpox until proven otherwise.

Patients who die of smallpox should be cremated whenever possible and mortuary workers should be vaccinated.

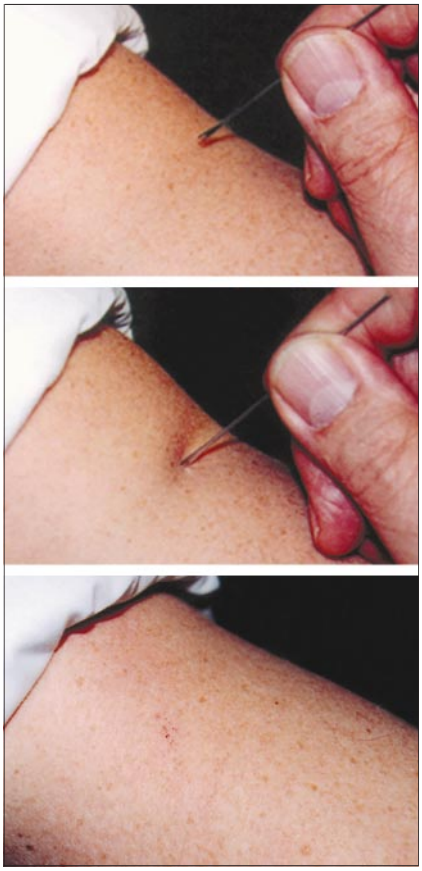
VACCINE ADMINISTRATION AND COMPLICATIONS

Smallpox vaccine is currently approved by the US Food and Drug Administration (FDA) for use only in persons in special-risk categories, including laboratory workers directly involved with smallpox or closely related orthopoxviruses. Under epidemic circumstances, widespread vaccination would be indicated, as recommended by the working group.

Vaccination has been successfully and safely administered to persons of all ages, from birth onward.[40] However, there are certain groups for whom elective vaccination has not been recommended be-

cause of the risk of complications. Under epidemic circumstances, however, such contraindications will have to be weighed against the grave risks posed by smallpox. If available, VIG can be administered concomitantly with vaccination to minimize the risk of complications in these persons.

Figure 3. Vaccination With the Bifurcated Needle



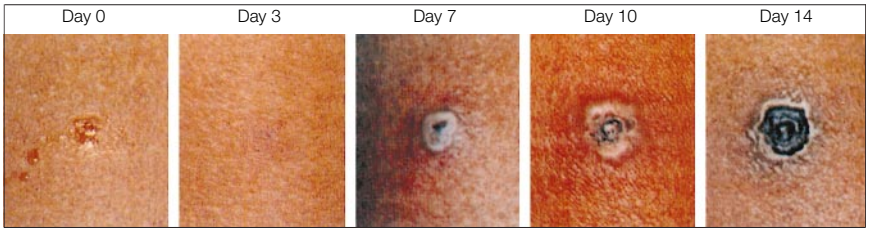
The requisite amount of reconstituted vaccine is held between the prongs of the needle and vaccination is done by multiple punctures; 15 strokes, at right angles to the skin over the deltoid muscle, are rapidly made within an area of about 5 mm in diameter.

Vaccination is normally performed using the bifurcated needle (FIGURE 3). A sterile needle is inserted into an ampoule of reconstituted vaccine and, on withdrawal, a droplet of vaccine sufficient for vaccination is held by capillarity between the 2 tines. The needle is held at right angles to the skin; the wrist of the vaccinator rests against the arm. Fifteen perpendicular strokes of the needle are rapidly made in an area of about 5 mm in diameter.[41,42] The strokes should be sufficiently vigorous so that a trace of blood appears at the vaccination site after 15 to 30 seconds. After vaccination, excess vaccine should be wiped from the site with gauze that should be discarded in a hazardous waste receptacle. The site should be covered with a loose, nonocclusive bandage to deter the individual from touching the site and perhaps transferring virus to other parts of the body.

After about 3 days, a red papule appears at the vaccination site and becomes vesicular on about the fifth day (FIGURE 4). By the seventh day, it becomes the typical Jennerian pustule—whitish, umbilicated, multilocular, containing turbid lymph and surrounded by an erythematous areola that may continue to expand for 3 more days. Regional lymphadenopathy and fever is not uncommon. As many as 70% of children have 1 or more days of temperature higher than 39°C (100°F) between days 4 and 14.[43] The pustule gradually dries, leaving a dark crust, which normally falls off after about 3 weeks.

A successful vaccination for those with partial immunity may manifest a gradient of responses. These range from what appears to be a primary take (as described herein) to an accelerated reaction in which there may be little more than a papule surrounded by erythema that reaches a peak between 3 and 7 days. A response that reaches a peak in erythema within 48 hours represents a hypersensitivity reaction and does not signify that growth of the vaccinia virus has occurred.[2] Persons exhibiting such a reaction should be revaccinated.

Figure 4. Typical Appearance of an Evolving Primary Vaccination Take



Reproduced with permission from the Centers for Disease Control and Prevention.[3]

Complications

The frequency of complications associated with use of the New York Board of Health strain (the strain used throughout the United States and Canada for vaccine) is the lowest for any established vaccinia virus strain, but the risks are not inconsequential.[44,45] Data on complications gathered by the CDC in 1968 are shown in TABLE 1. Complications occurred most frequently among primary vaccinees.

Postvaccinial Encephalitis. Postvaccinial encephalitis occurred at a rate of 1 case per 300 000 vaccinations and was observed only in primary vaccinees; one fourth of these cases were fatal and several had permanent neurological residua. Between 8 and 15 days after vaccination, encephalitic symptoms developed—fever, headache, vomiting, drowsiness, and, sometimes, spastic paralysis, meningitic signs, coma, and convulsions. Cerebrospinal fluid usually showed a pleocytosis. Recovery was either complete or associated with residual paralysis and other central nervous system symptoms and, sometimes, death. There was no treatment.

Progressive Vaccinia (Vaccinia Gangrenosa). Cases of progressive vaccinia occurred both among primary vaccinees and revaccinees. It was a frequently fatal complication among those with immune deficiency disorders. The vaccinial lesion failed to heal and progressed to involve adjacent skin with necrosis of tissue, spreading to other parts of the skin, to bones, and to viscera. Vaccinia immune globulin was used for this problem.[34,46] One case in a soldier with acquired immunodeficiency syndrome was successfully

treated with VIG and ribavirin. These treatment strategies were off-label and would be considered experimental.[26]

Eczema Vaccinatum. A sometimes serious complication, eczema vaccinatum occurred in some vaccinees and contacts with either active or healed eczema. Vaccinial skin lesions extended to cover all or most of the area once or currently afflicted with eczema. Vaccinia immune globulin was therapeutic.[46]

Generalized Vaccinia. A secondary eruption almost always following primary vaccination, generalized vaccinia resulted from blood-borne dissemination of virus. Lesions emerged between 6 and 9 days after vaccination and were either few in number or generalized. This complication was usually self-limited. In severe cases, VIG was indicated.[46]

Inadvertent Inoculation. Transmission to close contacts or autoinoculation to sites such as face, eyelid, mouth, and genitalia sometimes occurred. Most lesions healed without incident, although VIG was useful in some cases of periocular implantation.

Miscellaneous. Many different rashes have been associated with vaccination. Most common are erythema multiforme and variously distributed urticarial, maculopapular, and blotchy erythematous eruptions, which normally clear without therapy.

Groups at Special Risk for Complications

Consensus recommendations for special-risk groups as set forth herein reflect the best clinical and science-based judgment of the working group and do not necessarily correspond to FDA-approved uses.

Five groups of persons are ordinarily considered at special risk of smallpox vaccine complications: (1) persons with eczema or other significant exfoliative skin conditions; (2) patients with leukemia, lymphoma, or generalized malignancy who are receiving therapy with alkylating agents, antimetabolites, radiation, or large doses of corticosteroids; (3) patients with HIV infection; (4) persons with hereditary immune deficiency disorders; and (5) pregnant women. If persons with contraindications have been in close contact with a smallpox patient or the individual is at risk for occupational reasons, VIG, if available, may be given simultaneously with vaccination in a dose of 0.3 mL/kg of body weight to prevent complications. This does not alter vaccine efficacy. If VIG is not available, vaccine administration may still be warranted, given the far higher risk of an adverse outcome from smallpox infection than from vaccination.

VIG Therapy for Complications

Vaccinia immune globulin is valuable in treating patients with progressive vaccinia, eczema vaccinatum, severe generalized vaccinia, and periocular infections resulting from inadvertent inoculation. It is administered intramuscularly in a dose of 0.6 mL/kg of body weight. Because the dose is large (eg, 42 mL for a person weighing 70 kg), the product is given intramuscularly in divided doses over a 24- to 36-hour period and may be repeated, if necessary, after 2 to 3 days if improvement is not occurring.[47] Because the availability of VIG is so limited, its use should be reserved for the most serious cases. Vaccinia immune globulin, as well as vaccinia vaccine, is made available by the CDC through state health departments. Consultative assistance in the diagnosis and management of patients with complications can be obtained through state health departments.

DECONTAMINATION

Vaccinia virus, if released as an aerosol and not exposed to UV light, may persist for as long as 24 hours or somewhat longer under favorable conditions.[9] It is believed that variola virus would exhibit similar properties. However, by the time patients had become ill and it had been determined that an aerosol release of smallpox virus had occurred, there would be no viable smallpox virus in the environment. Vaccinia virus, if released as an aerosol, is almost completely destroyed within 6 hours in an atmosphere of high temperature (31°C-33°C) and humidity (80%) (TABLE 2).[9] In cooler temperatures (10°C-11°C) and lower humidity (20%), nearly two thirds of a vaccinia aerosol survives for as long as 24 hours.[9] It is believed that variola would behave similarly.

The occurrence of smallpox infection among personnel who handled laundry from infected patients is well documented[15] and it is believed that virus in such material remains viable for extended periods. Thus, special precautions need to be taken to ensure that all bedding and clothing of smallpox patients is autoclaved or laundered in hot water to which bleach has been added. Disinfectants that are used for standard hospital infection control, such as

Table 1. Complications of Smallpox Vaccination in the United States for 1968—Centers for Disease Control and Prevention National Survey[45]

Vaccination Status, Age, y	Estimated No. of Vaccinations	No. of Cases						
		Postvaccinial Encephalitis*	Progressive Vaccinia*	Eczema Vaccinatum*	Generalized Vaccinia	Accidental Infection	Other	Total
Primary vaccination†	5 594 000	16 (4)	5 (2)	58	131	142	66	418
Revaccination	8 574 000	0	6 (2)	8	10	7	9	40
Contacts	. . .‡	0	0	60 (1)	2	44	8	114
Total	**14 168 000**	**16 (4)**	**11 (4)**	**126 (1)**	**143**	**193**	**83**	**572**

*Data in parentheses indicate number of deaths attributable to vaccination.
†Data include 31 patients with unknown vaccination status.
‡Ellipses indicate contacts were not vaccinated.

hypochlorite and quaternary ammonia, are effective for cleaning surfaces possibly contaminated with virus.

Virus in scabs is more durable. At a temperature of 35°C and 65% relative humidity, the virus has persisted for 3 weeks.[48] At cooler temperatures (26°C), the virus has survived for 8 weeks at high relative humidity and 12 weeks at a relative humidity less than 10%.[48] Dutch investigators demonstrated that it was possible to isolate variola virus from scabs that had been sitting on a shelf for 13 years.[49] It is unlikely, however, that the smallpox virus, bound in the fibrin matrix of a scab, is infectious in humans. This is borne out by studies conducted during the eradication program and by surveillance for cases in newly smallpox-free areas.[2] It was reasoned that if the virus were able to persist in nature and infect humans, there would be cases occurring for which no source could be identified. Cases of this type were not observed. Rather, when cases were found, there were antecedent human cases with whom they had direct contact.

RESEARCH

Priority should be directed to 3 areas of smallpox research: vaccines, immunotherapy and drugs, and diagnostics.

The working group recommends that an emergency stockpile of at least 40 million doses of vaccine and a standby manufacturing capacity to produce more is a critical need. At a minimum, this quantity of vaccine would be needed in the control of an epidemic during the first 4 to 8 weeks after an attack. Smallpox vaccine, contained in glass-sealed ampoules and stored at –20°C, retains its potency almost indefinitely. However, several steps are necessary before manufacturing can begin. The traditional method for producing vaccine on the scarified flank of a calf is no longer acceptable because the product inevitably contains some microbial contaminants, however stringent the purification measures. Contemporary vaccines require the use of tissue cell cultures. Thus, as a first step, the traditional New York Board of Health strain needs to be grown in a suitable tissue cell culture and comparative studies performed of the reactogenicity and immunogenicity of calf-derived and tissue cell culture vaccines. This should be a comparatively straightforward exercise. The cost of such a stockpile should be comparatively modest because the vaccine would be packaged in 50-dose rather than costly single-dose containers. In the mid-1970s, 40 million doses would have cost less than $5 million (D.A.H., unpublished data, 1975).

The frequency of vaccine complications is sufficiently great to recommend development, if possible, of a more attenuated strain that, hopefully, would retain full efficacy. Development of an entirely new, genetically engineered strain would be both costly and time consuming. Moreover, it would be difficult at this time to justify its use in large numbers of human subjects to evaluate safety. There is, however, a candidate attenuated strain that was developed and field tested in Japan in the mid-1970s (a Lister strain–derived vaccine[50] that has been produced in volume in rabbit kidney cell culture and has been given to more than 100 000 persons in Japan). Research showed no severe complications among the first 30 000 vaccinees.[51] The cutaneous responses to vaccination were much less severe and far fewer vaccinees developed fever. More than 95% developed a Jennerian pustule; immunogenicity, as measured by neutralizing antibody, was slightly lower than for nonattenuated strains.

Vaccinia immune globulin has been used for the treatment of vaccine complications and for administration with vaccine to those for whom vaccine is otherwise contraindicated. Production of VIG should be a high priority for research. An alternative to VIG is also needed because VIG is difficult to produce and cumbersome to administer. Immunotherapy using humanized monoclonal antibodies is an alternative that should be explored. Studies of antiviral agents or drugs, already approved or near approval for marketing for use in other viral diseases, have suggested that 1 or more such products might prove useful.

Finally, a simple, rapid diagnostic test to identify variola virus in the oropharynx during the prodrome or early in the exanthematous phase of illness would be of considerable help in triage of suspected patients during the course of an outbreak.

Table 2. Viability of Vaccinia Virus in Aerosols at Various Intervals After Spraying[9]

Temperature, °C	Relative Humidity, %	Viable Vaccinia, %*			
		1 h	4 h	6 h	23 h
10.5-11.5	20	82	79	81	66
	50	83	92	77	59
	82-84	79	59	60	27
21.0-23.0	18-19	66	46	45	15
	48-51	86	57	50	12
	82-84	66	24	18	Trace
31.5-33.5	17-19	61	51	33	13
	50	51	26	15	Trace
	80-83	36	5.9	1.2	Trace

*Initial titer of $10^{7.7}$ plaque-forming units per milliliter of McIlvaine buffer, containing 1% dialyzed horse serum.

SUMMARY

The specter of resurgent smallpox is ominous, especially given the enormous efforts that have been made to eradicate what has been characterized as the most devastating of all the pestilential diseases. Unfortunately, the threat of an aerosol release of smallpox is real and the potential for a catastrophic scenario is great unless effective control measures can quickly be brought to bear.

Early detection, isolation of infected individuals, surveillance of contacts, and a focused selective vaccina-

tion program are the essential items of a control program. Educating health care professionals about the diagnostic features of smallpox should permit early detection; advance regionwide planning for isolation and care of infected individuals in their homes as appropriate and in hospitals when home care is not an option will be critical to deter spread. Ultimately, success in controlling a burgeoning epidemic will depend on the availability of adequate supplies of vaccine and VIG. An adequate stockpile of those commodities would offer a relatively inexpensive safeguard against tragedy.

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Disclaimers: In many cases, the indication and dosages and other information are not consistent with current FDA-approved labeling. The recommendations on the use of drugs and vaccine for uses not approved by the FDA do not represent the official views of the FDA or of any of the federal agencies whose scientists participated in these discussions. Unlabeled uses of the products recommended are noted in the sections of this article in which these products are discussed. Where unlabeled uses are indicated, information used as the basis for the recommendations is discussed.

The views, opinions, assertions, and findings contained herein are those of the authors and should not be construed as official US Department of Defense or US Department of Army positions, policies, or decisions unless so designated by other documentation.

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PLACER COUNTY

HEALTH AND HUMAN SERVICES

COMMUNICABLE DISEASE CONTROL

Medical Treatment and Response to Suspected Smallpox:

Information for Health Care Providers During Biologic Emergencies

ALL SUSPECT CASES OF SMALLPOX MUST BE REPORTED IMMEDIATELY TOTHE PLACER COUNTY HEALTH AND HUMAN SERVICES, COMMUNICABLE DISEASE CONTROL:

During Business Hours: (530) 889-7141

After Hours (Nights, Weekends and Holidays): Health Officer Richard J. Burton, M.D., M.P.H., at (530) 889-7119

(In the event that you are unable to reach a Communicable Disease Control Contact, please call the Placer County Office of Emergency Services at (530) 886-5300 or the 24-hour dispatch at (530) 886-5375).

I. KEY SUMMARY POINTS

Epidemiology:

- Highly infectious after aerosolization
- Person-to-person transmission can occur via droplet nuclei or aerosols expelled from the oropharynx and by direct contact
- Contaminated clothing or bed linens can also spread the virus
- About 30% of susceptible contacts will become infected

Clinical:

- Incubation period is 12-14 days (ranges 7-17 days)
- Characteristic rash appears 2-3 days after nonspecific, flu-like prodrome (fever and headache)
- Maculopapular rash begins on mucosa of mouth and pharynx, face, hands, forearms and spreads to legs and centrally to trunk; lesions are more predominant on the face and extremities than on the trunk.
- Lesions progress synchronously on any given part of the body from macules to papules to vesicles to pustules to crusty scabs

Laboratory Diagnosis:

- Mask and gloves should be worn by person obtaining specimen, preferably a person who has been recently vaccinated
- Vesicular fluid is obtained by opening lesions with the blunt edge of a scalpel, harvesting fluid with a cotton swab; scabs can be removed by forceps. Swabs and scabs should be placed in a vacutainer, sealed with tape, and placed in a second, durable, watertight container
- Laboratory specimens must be handled in a Biosafety Level 4 facility (e.g. CDC) and will be evaluated with electron microscopy and cell culture.
- Contact the Placer County Public Health Laboratory at (530) 889-7205 for assistance.

Patient Isolation:

- Strict isolation in negative pressure room (high efficiency particulate air filtration ideal) from onset of rash until all scabs separate
- Laundry and waste should be autoclaved before being laundered or incinerated

Treatment:

- Supportive care is the mainstay of therapy
- In-vitro antiviral activity against poxviruses has been shown with adefovir, cidofovir, dipivoxil, and ribavirin. (Animal studies suggest that cidofovir may be most effective).

Prophylaxis:

- Smallpox vaccine would be required for all persons exposed at the time of the bioterrorist attack or anyone with close personal contact with a smallpox case
- Vaccine is most effective if given before of within 3 days of exposure

Ideally, all exposed persons should be placed in strict quarantine for 17 days after last contact with a smallpox case

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After Hours (Nights, Weekends and Holidays): Health Officer Richard J. Burton, M.D., M.P.H., at (530) 889-7119

(In the event that you are unable to reach a Communicable Disease Control Contact, please call the Placer County Office of Emergency Services at (530) 886-5300 or the 24-hour dispatch at (530) 886-5375).

II. Introduction/Epidemiology

Smallpox is caused by an *Orthopoxvirus*, variola, a large enveloped DNA virus. The last occurrence of endemic smallpox was in Somalia in 1977 and the last human cases were laboratory-acquired infections in 1978. Smallpox was declared eradicated in 1980 by the World Health Organization.

Variola is infectious only for humans; there is no animal reservoir. Other key epidemiologic points include:

- The virus is highly stable and retains infectivity for long periods outside the host. Historically, smallpox was more common in the winter and spring; with aerosol infectivity decreasing with higher temperatures and humidity.
- Approximately 30% of susceptible contacts became infected during the era of endemic smallpox.
- Smallpox is transmitted by respiratory secretions, most efficiently during the early stages of the rash illness; it is generally believed that close person-to-person proximity is required for reliable transmission to occur. Patients are considered infectious from the time of development of the eruptive exanthem (usually 2-3 days after fever begins) until all scabs separate. In addition, virus can readily be recovered from scabs throughout convalescence.
- Fomites and inanimate objects are considered potential vehicles of transmission. However, since laundry from infected patients may contain viable virus, bedding and clothing of smallpox patients should be autoclaved.
- **Patients with confirmed or suspected smallpox should be placed on strict isolation until no longer considered infectious.**
- **Strict quarantine with respiratory isolation for 17 days is recommended for all persons in direct contact with a case.** In the setting of a large outbreak due to bioterrorism, this may not be possible - in which case, quarantine of exposed persons in their home with a daily fever watch may be an alternative public health measure.

During the past century, the prototypical disease, variola major, caused mortality of 3% and 30% in the vaccinated and unvaccinated, respectively. The key to control and eventual eradication of endemic smallpox was vigorous case identification, followed by quarantine and immunization of contacts. Routine smallpox vaccination was discontinued in the United States in 1972. Immunity from prior smallpox vaccination wanes with time and at this point, the entire United States' civilian population is likely susceptible. However, persons who have been vaccinated in the past may experience less severe disease.

III. Significance as a Potential Bioterrorist Agent

- High aerosol infectivity; stability of virus in aerosols

- Infectious dose is thought to be low (as low as a few virions)
- Increasing susceptibility of the population
- High mortality rate in the non-immune
- Potential for significant ongoing transmission due to secondary spread
- Ease of large-scale virus production
- Existence of clandestine smallpox virus stockpiles outside the stockpiles at the Centers for Disease Control and Prevention (USA) and the State Center for Virology and Biotechnology (Koltsovo, Russia).
- Currently, worldwide supplies of smallpox vaccine are limited

IV. Clinical Manifestations

During an act of bioterrorism, release of an aerosol will be the most likely route of transmission.

A. Variola major

***Incubation period* - typically 12-14 days, can be 7-17 days**

Symptoms:

Prodrome: Acute onset of malaise, fever, rigors, vomiting, headache and backache. 15% develop delirium. 10% of light skinned patients have an erythematous rash.

Appears as soon as 2-3 days after prodrome, just as fever peaks.

Discrete maculopapular rash on face, hands, forearms, and mucous membranes of mouth and pharynx. Involvement of palms and soles is common.

Exanthem: Rash spreads to legs and then centrally to trunk during Week 2. Lesions quickly progress from macules to papules to vesicles to pustular vesicles (umbilicated) to crusty scabs.

Scabs form 8-14 days after onset, leaving depressions and depigmented scars primarily on the face which has more sebaceous glands.

CLINICAL CLUES TO DISTINGUISH SMALLPOX FROM CHICKENPOX:

- Smallpox has many more lesions on face and extremities than trunk (Centrifugal spread).
- Smallpox lesions are synchronous in their stage of development.
- Smallpox lesions are more common on palms and soles.
- Smallpox lesions are more deeply imbedded in the dermis compared with the superficial lesions of chickenpox.

B. Variations in Variola Major

Flat-type/"malignant" smallpox: Occurs in 2-5% of smallpox cases due to lack of adequate cell-mediate immune response. Notable for severe systemic toxicity and slow evolution of flat, soft, focal skin lesions. These papules coalesce and never become pustular. Skin develops a fine-grained reddish color, resembling crepe rubber. The mortality among unvaccinated persons is 95%.

Hemorrhagic-type smallpox: Occurs in < 3% of smallpox cases. Notable for extensive petechia, mucosal hemorrhage and intense toxemia (high fevers, headache, backache and abdominal pain). Seen more commonly in pregnant women. Patients usually die before development of typical pox lesions. Differential diagnosis includes: meningococcemia and acute leukemia.

C. Variola minor (alastrim)

Incubation period - 7-17 days

Symptoms - Clinically resembles variola major but with milder systemic toxicity and sometimes more diminutive pox lesions. Lesions on the face are typically more sparse and evolve more rapidly than those on the arms and legs. Mortality in the unvaccinated is usually less than 1%.

D. Clinical Complications of Smallpox

Arthritis and osteomyelitis:	Frequency is 1-2%. Occurs late in course; usually affects children; bilateral elbow joint involvement most common.
Cough and bronchitis:	Occasionally a prominent symptom. Pneumonia was unusual.
Pulmonary edema:	Common in hemorrhagic and flat-type smallpox.
Orchitis:	Noted in 0.1% of patients.
Encephalitis:	Developed in 1 in 500 patients with variola major.
Keratitis/corneal ulcers:	Progresses to blindness in about 1% of cases.
Disease during pregnancy:	Precipitated high perinatal mortality.

E. Monkeypox

A naturally-occurring relative of variola, monkeypox virus, is a rare zoonosis that occurs in the rain forest areas of Africa and is felt to be rodent borne. The disease it causes, monkeypox, is clinically indistinguishable from smallpox, except for notable swelling of cervical and inguinal lymph nodes.

V. **Laboratory Diagnosis**

If smallpox is suspected, please call the Placer County Public Health Laboratory at (530)-889-7205 to arrange for submission of specimens to CDC for testing. After hours, please call Placer County Health Officer Richard J. Burton, M.D., M.P.H., at (530) 889-7119.

In the event that you are unable to reach a Communicable Disease Control Contact, please call the Placer County Office of Emergency Services at (530) 886-5300 or the 24-hour dispatch at (530) 886-5375

The diagnosis of smallpox requires astute clinical evaluation. The clinical diagnosis may be confused with chickenpox, erythema multiforme with bullae or allergic contact dermatitis.

The diagnosis of smallpox is an international emergency and confirmation of the diagnosis by laboratory techniques requires coordination between the medical and laboratory community and local, state, federal and international agencies. **If you clinically suspect even a single case of smallpox, notify the Placer County Health**

and Human Services, Communicable Disease Control IMMEDIATELY at (530) 889-7141 (AFTER HOURS CALL Health Officer Richard J. Burton, M.D., M.P.H., at (530) 889-7119).

In the event of a bioterrorist release of smallpox, confirmation by a reference laboratory will be necessary for the earliest (index) cases. After a smallpox outbreak is confirmed, diagnosis of subsequent cases will need to be based on a compatible clinical presentation.

Opening the lesions with the blunt edge of a sterile scalpel and harvesting the fluid with a sterile swab should obtain vesicular fluid. The swab(s) should be placed in a cryo-safe 1-2 ml gasketed vial (the gasket on the vial prevents gas exchange, e.g., carbon dioxide vapors from dry ice, which can acidify samples). Scabs can be removed with forceps and also placed in a gasketed vial. The vial should not contain any transport medium. In addition, a droplet of vesicular fluid can be placed on a clean microscopic slide and allowed to air dry in a safe location. The slides should be placed in an airtight container. Specimens from different patients should not be mixed together. All specimens should be safely secured for shipping. Specimens will be tested at the CDC's Biosafety Level 4 reference laboratory using the following tests: (Contact the Placer County Public Health Laboratory at (530) 889-7205 for assistance)

- **Light or Electronic Microscopy**
  Scrapings of vesicular lesions can be examined by electron microscopy for characteristic brick-shaped virions. This method does not distinguish variola from vaccinia, monkeypox or cowpox.

- **Viral cultures**
  Requires isolation of virus and characterization of its growth on chorioallantoic membrane or cell culture.

- **Other Testing**
  Polymerase chain reaction and restriction fragment length polymorphisms (RFLP) diagnostic techniques promise a more accurate and less cumbersome method of identifying variola virus. These techniques are currently only available at national reference laboratories, such as the CDC.

VI. Handling Laboratory Specimens

All other laboratory tests should be performed in Biological Safety Level 2 cabinets and blood cultures should be maintained in a closed system. Laboratory staff handling specimens from persons who might have smallpox must wear surgical gloves, protective gowns and shoe covers. Every effort should be made to avoid splashing or creating an aerosol, and protective eye wear and masks should be worn if work cannot be done in a Biological Safety Level 2 cabinet. A full-face mask respirator with a HEPA (high efficiency particulate air) filter is an acceptable, but cumbersome, alternative to masks and protective eye wear. Laboratories working with a large amount of viral organisms should use Biological Safety Level 3 cabinets.

Accidental spills of potentially contaminated material should be decontaminated immediately by covering liberally with a disinfectant solution (1% sodium hypochlorite or sodium hydroxide (0.1N)). All biohazardous waste should be decontaminated by autoclaving. Contaminated equipment or instruments may be decontaminated with a hypochlorite solution, 1% peracetic acid, formaldehyde, ethylene oxide, copper irradiation, or other O.S.H.A. approved solutions, or by autoclaving or boiling for 10 minutes.

VII. Treatment

Supportive care is the mainstay of therapy.

Currently, there are no anti-viral drugs of proven efficacy. Although, adefovir, dipivoxil, cidofovir and ribavirin have significant in vitro antiviral activity against poxviruses, their efficacy as therapeutic agents for smallpox is currently uncertain. Cidofovir is FDA-licensed and shows the most promise in animal models.

VIII. Isolation of Patients

Smallpox is transmissible from person-to-person by exposure to respiratory secretions (particularly from coughing patients), contact with pox lesions and by fomites (although not efficiently). All staff should observe **both Airborne and Contact Precautions**, in addition to Standard Precautions, when caring for patients with suspected or confirmed smallpox.

Patients should be placed in a closed-door, negative pressure room with 6 to 12 air exchanges per hour and HEPA filtration of exhausted air. Patients with smallpox should be placed on strict isolation from the onset of eruptive exanthem until all pox scabs have

separated (generally 14-28 days). Healthcare workers and others entering the room should wear appropriate respiratory protection; respiratory masks should meet the minimal NIOSH standard for particulate respirators (N95). Healthcare provides should wear clean gloves and gowns for all patient contact.

In the event of a large-scale smallpox outbreak due to a bioterrorist attack, there may be massive numbers of victims. In this case, there may be a need to cohort patients due to limited availability of respiratory isolation rooms. If this is done, then all patients should receive smallpox vaccine or vaccine immune globulin within 3 days of exposure, if available, in the event that some of these patients are misdiagnosed with smallpox.

All healthcare workers providing direct patient care to persons with smallpox should be vaccinated. If vaccine is unavailable, then only staff who previously received smallpox vaccine (*e.g., persons born before 1972 or persons who were in the military before 1989*) should be caring for patients with smallpox.

IX. Disposal of Infectious Waste

Use of tracking forms, containment, storage, packaging, treatment and disposal methods should be based upon the same rules as all other regulated medical wastes.

X. Autopsy and Handling of Corpses

All postmortem procedures are to be performed using Universal Precautions. In addition, due to concerns about aerosolization of the virus, personnel should use particulate respirators as recommended under **Strict Isolation** precautions.

- All persons performing or assisting in postmortem procedures must wear mandated P.P.E. (personal protective equipment) as delineated by O.S.H.A. guidelines.
- Instruments should be autoclaved or sterilized with a 10% bleach solution or other solutions approved by O.S.H.A. Surfaces contaminated during postmortem procedures should be decontaminated with an appropriate chemical germicide such as 10% hypochlorite or 5% phenol (carbolic acid).

XI. Management of Exposed Persons

An exposed person is defined as a person who has been in close personal contact with a patient with suspect or confirmed smallpox. **Close personal contact** includes persons

residing in the same household with the case-patient or persons with face-to-face contact with the case AFTER the case developed febrile illness. (During outbreaks in Europe in the 1960's, up to 10-20 secondary cases occurred after exposure to a single case-patient, if vaccination efforts were delayed.)

- **Quarantine**: All exposed persons should be placed in strict quarantine with respiratory isolation for 17 days after last contact with suspect or confirmed smallpox case(s). In the setting of a large outbreak due to bioterrorism, this may not be possible - in which case, quarantine of exposed persons in their home with a daily fever watch may be an alternative public health measure.

- **Vaccination**:

  Vaccine: In the United States, the smallpox vaccine supply is overseen by the CDC. The Wyeth vaccine (using the New York Board of Health vaccinia strain) is freeze-dried in multidose vials (50 doses per vial) at 20 ^{o}C.

  Vaccine Indications: All exposed persons, including all household and face-to-face contacts of patients, should be vaccinated immediately, if vaccine is available. Additionally, all health care workers that might care for smallpox patients, emergency personnel who might transport patients, and mortuary staff should be vaccinated, if vaccine is available. **Vaccination is most effective at protecting against smallpox if given within 3 days of exposure.**

  Methodology: A bifurcated needle is inserted into an ampule of reconstituted vaccine and, on withdrawal, a droplet of vaccine is held by capillarity between the two tines. The needle is held at right angles to the skin, the wrist of the vaccinator rests against the arm. Fifteen up and down (perpendicular) strokes of the needle are rapidly made in an area of 5-mm diameter. The strokes should be sufficiently vigorous so that a trace of blood appears at the vaccination site after 15-30 seconds. Excess vaccine should be wiped from the site with gauze (gauze should be discarded into a hazardous waste receptacle) and the site covered with a loose, non-occlusive bandage.

  Evaluation of vaccine response:

  (1) Primary vaccine response (never previously vaccinated):

  Day 3: A red papule appears at the vaccination site

  Day 5: Papule becomes vesicular

  Day 7: A whitish, umbilicated, multilocular pustule develops, containing turbid lymph and surrounded by an erythematous areola which may expand further for

3 days. Fever during days 4-14, particularly for children, is common. The pustule dries and falls off after about 3 weeks.

(2) Re-immunization response (those previously vaccinated): May react as described above, or may have a papule surrounded by erythema that peaks between 3 and 7 days. A response that peaks within 48 hours is a hypersensitivity reaction; patients with this reaction should be revaccinated.

- **Contraindications to Vaccination**:
  - Eczema or other exfoliative skin condition (*e.g., atopic dermatitis, burns, impetigo*)
  - Leukemia, lymphoma, generalized malignancy or chemotherapy with alkylating agents, antimetabolites, radiation or high dose corticosteroids
  - HIV infection or AIDS
  - Hereditary immune deficiency disorders
  - Pregnant women
  - Life-threatening allergy to polymyxin B, streptomycin, tetracycline or neomycin.

In the setting of a large bioterrorist attack, the risk of vaccination must be weighed against the likelihood of acquiring infection. If VIG (vaccinia immune globulin) is available, those in close personal contact with a smallpox case AND with a clear contraindication to vaccine may receive vaccine PLUS VIG (0.3 ml/kg of body weight) simultaneously within the first week following exposure.

- **Potential Side-Effects of Vaccination**:

Side effects include: low grade fever, lymphadenopathy, autoinoculation, secondary inoculation, ocular vaccinia, urticarial rash, Stevens-Johnson syndrome, generalized vaccinia (3 per 10,000 vaccinations occurring from 6-9 days after vaccination), eczema vaccinatum, progressive vaccinia (1 per million vaccinations) and postvaccinial encephalitis (3 per million primary vaccinations occurring from 8-15 days after vaccination).

Severe vaccine complications should be treated with VIG (0.6 ml/kg body weight). The dose should be administered intramuscularly in 2 divided

doses over a 24 to 36 hour period. The dose can be repeated in 2-3 days, if needed.

XII. Reporting to the Health Department

Smallpox is an international emergency and even an isolated suspect case must be reported immediately to the Placer County Health and Human Services, Communicable Disease Control .

All suspect cases should be immediately reported **by telephone** to:

- **During business hours**
  Placer County Health and Human Services Communicable Disease Control at (530) 889-7141

- **After business hours**
  Placer County Health Officer Richard J. Burton, M.D., M.P.H., at (530) 889-7119

- In the event that you are unable to reach a Communicable Disease Control Contact, please call the Placer County Office of Emergency Services at (530) 886-5300 or the 24-hour dispatch at (530) 886-5375

XIII. References

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ANTHRAX

ALL SUSPECT CASES OF ANTHRAX MUST BE REPORTED IMMEDIATELY TO THE HEALTH AND HUMAN SERVICES COMMUNICABLE DISEASE CONTROL:

During business hours: (530) 889-7141
After hours (Health Officer Richard J. Burton, M.D., M.P.H.): (530) 889-7119

(In the event that you are unable to reach a Communicable Disease Control Contact, please call the Placer County Office of Emergency Services at (530) 886-5300 during business hours, or 24-hour dispatch at (530) 886-5375 after business hours.)

Epidemiology:

- Anthrax can be transmitted by inhalation, ingestion, or inoculation (inhalation is the most likely during a bioterrorist attack)
- The spore form of anthrax is highly resistant to physical and chemical agents; spores can persist in the environment for years
- **Anthrax is not transmitted from person to person**

Clinical:

- Incubation period is 1-5 days (range up to 43 days)
- Inhalation anthrax presents as acute hemorrhagic mediastinitis
- Biphasic illness, with initial phase characterized by nonspecific flu-like illness followed by acute phase characterized by acute respiratory distress and toxemia (sepsis)
- Chest x-ray findings: **Mediastinal widening in a previously healthy patient in the absence of trauma is pathognomonic for anthrax**
- Mortality rate for inhalation anthrax approaches 90%, even with treatment. Shock and death within 24 – 36 hours

Laboratory Diagnosis:

- Laboratory specimens should be handled in a Biosafety Level 2 facility (e.g. California state Microbial Diseases Laboratory)
- Gram stain shows gram positive bacilli, occurring singly or in short chains, often with squared off ends (safety pin appearance). In advanced disease, a gram stain of unspun blood may be positive
- Distinguishing characteristics on culture include: non-hemolytic, non-motile, capsulated bacteria that are susceptible to gamma phage lysis
- ELISA and PCR tests are available at national reference laboratories
- Fluorescent antibody test available through the Laboratory Response Network.
- Contact the Placer County Public Health Laboratory for assistance.

Patient Isolation:

- Standard barrier isolation precautions. Patients do not require isolation rooms
- **Anthrax is not transmitted person to person**

Treatment:

- Prompt initiation of antibiotic therapy is essential
- Antibiotic susceptibility testing is KEY to guiding treatment
- Ciprofloxicin (400 mg IV q 12 hr) is the antibiotic of choice for penicillin-resistant anthrax or for empiric therapy while awaiting susceptibility results

Anthrax as a Biological Weapon
Medical and Public Health Management

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Objective To develop consensus-based recommendations for measures to be taken by medical and public health professionals following the use of anthrax as a biological weapon against a civilian population.

Participants The working group included 21 representatives from staff of major academic medical centers and research, government, military, public health, and emergency management institutions and agencies.

Evidence MEDLINE databases were searched from January 1966 to April 1998, using the Medical Subject Headings *anthrax*, *Bacillus anthracis*, *biological weapon*, *biological terrorism*, *biological warfare*, and *biowarfare*. Review of references identified by this search led to identification of relevant references published prior to 1966. In addition, participants identified other unpublished references and sources.

Consensus Process The first draft of the consensus statement was a synthesis of information obtained in the formal evidence-gathering process. Members of the working group provided formal written comments which were incorporated into the second draft of the statement. The working group reviewed the second draft on June 12, 1998. No significant disagreements existed and comments were incorporated into a third draft. The fourth and final statement incorporates all relevant evidence obtained by the literature search in conjunction with final consensus recommendations supported by all working group members.

Conclusions Specific consensus recommendations are made regarding the diagnosis of anthrax, indications for vaccination, therapy for those exposed, postexposure prophylaxis, decontamination of the environment, and additional research needs.

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OF THE NUMEROUS BIOLOGICAL agents that may be used as weapons, the Working Group on Civilian Biodefense has identified a limited number of organisms that could cause disease and deaths in sufficient numbers to cripple a city or region. Anthrax is one of the most serious of these diseases.

High hopes were once vested in the Biological Weapons and Toxins Convention, which prohibited offensive biological weapons research or production and was signed by most countries. However, Iraq and the former Soviet Union, both signatories of the convention, have subsequently acknowledged having offensive biowarfare programs; a number of other countries are believed to have such programs, as have some autonomous terrorist groups. The possibility of a terrorist attack using bioweapons would be especially difficult to predict, detect, or prevent, and thus, it is among the most feared terrorist scenarios.[1]

Biological agents have seldom been dispersed in aerosol form, the exposure mode most likely to inflict widespread disease. Therefore, historical experience provides little information about the potential impact of a biological attack or the possible efficacy of postattack measures such as vaccination, antibiotic therapy, or quarantine. Policies and strategies must therefore rely on interpretation and extrapolation from an incomplete knowledge base. The Working Group on Civilian Biodefense reviewed the available literature and expertise and developed consensus recommendations for medical and public health measures to be taken following such an attack.

CONSENSUS METHODS

The working group comprised 21 representatives from academic medical cen-

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The first draft of the working group's consensus statement was the result of synthesis of information obtained in the formal evidence-gathering process. Members of the working group were asked to make formal written comments on this first draft of the document in May 1998. Suggested revisions were incorporated into the second draft of the statement. The working group was convened to review the second draft of the statement on June 12, 1998, at the Johns Hopkins Center for Civilian Biodefense Studies, Baltimore, Md. Consensus recommendations were made; no significant disagreements existed at the conclusion of this meeting. The third draft incorporated changes suggested at the conference and working group members had an additional opportunity to review the draft and suggest final revisions. The final statement incorporates all relevant evidence obtained by the literature search in conjunction with final consensus recommendations supported by all working group members. Funding for the development of the working group consensus statement was primarily provided by each representative's institution or agency. The Office of Emergency Preparedness, Department of Health and Human Services (DHHS), provided travel funds for 4 members of the group.

The assessment and recommendations provided herein represent the best professional judgment of the working group based on data and expertise currently available. The conclusions and recommendations need to be regularly reassessed as new information becomes available.

HISTORY OF CURRENT THREAT

For centuries, anthrax has caused disease in animals and, uncommonly, serious illness in humans throughout the world.[2] Research on anthrax as a biological weapon began more than 80 years ago.[3] Today, at least 17 nations are believed to have offensive biological weapons programs[4]; it is uncertain how many are working with anthrax. Iraq has acknowledged producing and weaponizing anthrax.[5]

Most experts concur that the manufacture of a lethal anthrax aerosol is beyond the capacity of individuals or groups without access to advanced biotechnology. However, autonomous groups with substantial funding and contacts may be able to acquire the required materials for a successful attack. One terrorist group, Aum Shinrikyo, responsible for the release of sarin in a Tokyo, Japan, subway station in 1995,[6] dispersed aerosols of anthrax and botulism throughout Tokyo on at least 8 occasions. For unclear reasons, the attacks failed to produce illness.[7]

The accidental aerosolized release of anthrax spores from a military microbiology facility in Sverdlovsk in the former Soviet Union in 1979 resulted in at least 79 cases of anthrax infection and 68 deaths and demonstrated the lethal potential of anthrax aerosols.[8] An anthrax aerosol would be odorless and invisible following release and would have the potential to travel many kilometers before disseminating.[9,10] Evidence suggests that following an outdoor aerosol release, persons indoors could be exposed to a similar threat as those outdoors.[11]

In 1970, a World Health Organization (WHO) expert committee estimated that casualties following the theoretical aircraft release of 50 kg of anthrax over a developed urban population of 5 million would be 250 000, 100 000 of whom would be expected to die without treatment.[9] A 1993 report by the US Congressional Office of Technology Assessment estimated that between 130 000 and 3 million deaths could follow the aerosolized release of 100 kg of anthrax spores upwind of the Washington, DC, area—lethality matching or exceeding that of a hydrogen bomb.[12] An economic model developed by the Centers for Disease Control and Prevention (CDC) suggested a cost of $26.2 billion per 100 000 persons exposed.[13]

EPIDEMIOLOGY

Naturally occurring anthrax is a disease acquired following contact with anthrax-infected animals or anthrax-contaminated animal products. The disease most commonly occurs in herbivores, which are infected by ingesting spores from the soil. Large anthrax epizootics in herbivores have been reported; during a 1945 outbreak in Iran, 1 million sheep died.[14] Animal vaccination programs have reduced drastically the animal mortality from the disease.[15] However, anthrax spores continue to be documented in soil samples from throughout the world.[16-18]

In humans, 3 types of anthrax infection occur: inhalational, cutaneous, and gastrointestinal. Naturally occurring inhalational anthrax is now a rare cause of human disease. Historically, wool sorters at industrial mills were at highest risk. Only 18 cases were reported in the United States from 1900 to 1978, with the majority occurring in special-risk groups, including goat hair mill or goatskin workers and wool or tannery workers. Two of the 18 cases were laboratory associated.[19]

Cutaneous anthrax is the most common naturally occurring form, with an estimated 2000 cases reported annually.[18] Disease typically follows exposure to anthrax-infected animals. In the United States, 224 cases of cutaneous anthrax were reported between 1944 and 1994.[20] The largest reported epidemic occurred in Zimbabwe between 1979 and 1985, when more than 10 000 human cases of anthrax were reported, nearly all of them cutaneous.[21]

Gastrointestinal anthrax is uncommonly reported.[18,22,23] However, gastrointestinal outbreaks have been reported

in Africa and Asia.[24] Gastrointestinal anthrax follows ingestion of insufficiently cooked contaminated meat and includes 2 distinct syndromes, oral-pharyngeal and abdominal.[22,24-27] In 1982, there were 24 cases of oral-pharyngeal anthrax in a rural northern Thailand outbreak following the consumption of contaminated buffalo meat.[24] In 1987, there were 14 cases of gastrointestinal anthrax reported in northern Thailand with both oral-pharyngeal and abdominal disease occurring.[25]

No case of inhalational anthrax has been reported in the United States since 1978,[19,20] making even a single case a cause for alarm today. As was demonstrated at Sverdlovsk in 1979, inhalational anthrax is expected to account for most morbidity and essentially all mortality following the use of anthrax as an aerosolized biological weapon.[8,28] In the setting of an anthrax outbreak resulting from an aerosolized release, cutaneous anthrax would be less common than inhalational anthrax, easier to recognize, simpler to treat, and associated with a much lower mortality. In the Sverdlovsk experience, there were no deaths in patients developing cutaneous anthrax.[8] There is little information available about the risks of direct contamination of food or water with anthrax spores. Although human infections have been reported, experimental efforts to infect primates by direct gastrointestinal instillation of anthrax spores have not been successful.[29]

MICROBIOLOGY

Bacillus anthracis derives from the Greek word for coal, *anthrakis*, because the disease causes black, coal-like skin lesions. *Bacillus anthracis* is an aerobic, gram-positive, spore-forming, nonmotile *Bacillus* species. The nonflagellated vegetative cell is large (1-8 µm in length, 1-1.5 µm in breadth). Spore size is approximately 1 µm. Spores grow readily on all ordinary laboratory media at 37°C, with a "jointed bamboo-rod" cellular appearance and a unique "curled-hair" colonial appearance, and display no hemolysis on sheep agar (FIGURE 1). This cellular and colonial morphology theoretically should make its identification by an experienced microbiologist straightforward, although few practicing microbiologists outside the veterinary community have seen anthrax colonies other than in textbooks.[30]

Anthrax spores germinate when they enter an environment rich in amino acids, nucleosides, and glucose, such as that found in the blood or tissues of an animal or human host. The rapidly multiplying vegetative anthrax bacilli, on the contrary, will only form spores after local nutrients are exhausted, such as when anthrax-infected body fluids are exposed to ambient air.[16,17] Full virulence requires the presence of both an antiphagocytic capsule and 3 toxin components (ie, protective antigen, lethal factor, and edema factor).[30] Vegetative bacteria have poor survival outside of an animal or human host; colony counts decline to undetectable within 24 hours following inoculation into water.[17] This contrasts with the environmentally hardy properties of the *B anthracis* spore, which can survive for decades.[30]

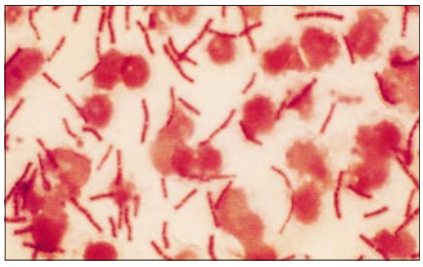
PATHOGENESIS AND CLINICAL MANIFESTATIONS

Inhalational Anthrax

Inhalational anthrax follows deposition of spore-bearing particles of 1 to 5 µm into alveolar spaces.[31,32] Macrophages ingest the spores, some of which undergo lysis and destruction. Surviving spores are transported via lymphatics to mediastinal lymph nodes, where germination may occur up to 60 days later.[28,29,33] The process responsible for the delayed transformation of spores to vegetative cells is poorly understood but well documented. In Sverdlovsk, cases occurred from 2 to 43 days after exposure.[8] In experimental monkeys, fatal disease occurred up to 58 days[28] and 98 days[34] after exposure. Viable spores have been demonstrated in the mediastinal lymph nodes of monkeys 100 days after exposure.[35]

Once germination occurs, disease follows rapidly. Replicating bacteria release toxins leading to hemorrhage, edema, and necrosis.[23,36] In experimental animals, once toxin production has reached critical threshold, death occurs even if sterility of the bloodstream is achieved with antibiotics.[19] Based on primate data, it has been estimated that for humans the LD 50 (lethal dose sufficient to kill 50% of persons exposed to it) is 2500 to 55 000 inhaled anthrax spores.[37]

Figure 1. Gram Stain of *Bacillus anthracis*



Gram-positive anthrax bacilli in a peripheral blood smear from a rhesus monkey that died of inhalational anthrax. Reprinted with permission from Zajtchuk and Bellamy.[23]

The term *inhalational anthrax* reflects the nature of acquisition of the disease. The term *anthrax pneumonia* is misleading. Typical bronchopneumonia does not occur. Postmortem pathological study of patients who died because of inhalational anthrax in Sverdlovsk showed hemorrhagic thoracic lymphadenitis and hemorrhagic mediastinitis in all patients. In up to half of the patients, hemorrhagic meningitis also was seen. No patients who underwent autopsy had evidence of a bronchoalveolar pneumonic process, although 11 of 42 patients undergoing autopsy had evidence of a focal, hemorrhagic, necrotizing pneumonic lesion analogous to the Ghon complex associated with tuberculosis.[38] These findings are consistent with other human case series and experimentally induced inhalational anthrax in animals.[33,39,40]

Early diagnosis of inhalational anthrax would be difficult and would require a high index of suspicion. Clinical information is available from only some of the 18 cases reported in the United States in this century and from the limited available information from Sverdlovsk. The clinical presentation has been described as a 2-stage illness. Pa-

tients first developed a spectrum of nonspecific symptoms, including fever, dyspnea, cough, headache, vomiting, chills, weakness, abdominal pain, and chest pain.[8,19] Signs of illness and laboratory studies were nonspecific. This stage of illness lasted from hours to a few days. In some patients, a brief period of apparent recovery followed. Other patients progressed directly to the second, fulminant stage of illness.[2,19,41]

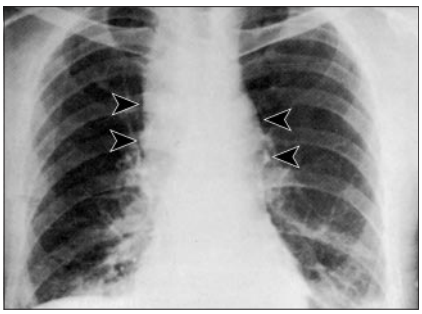
This second stage developed abruptly, with sudden fever, dyspnea, diaphoresis, and shock. Massive lymphadenopathy and expansion of the mediastinum led to stridor in some cases.[42,43] A chest radiograph most often showed a widened mediastinum consistent with lymphadenopathy (FIGURE 2).[42] Up to half of patients developed hemorrhagic meningitis with concomitant meningismus, delirium, and obtundation. In this second stage of illness, cyanosis and hypotension progress rapidly; death sometimes occurs within hours.[2,19,41]

The mortality rate of occupationally acquired cases in the United States is 89%, but the majority of cases occurred before the development of critical care units and, in some cases, before the advent of antibiotics.[19] At Sverdlovsk, it is reported that 68 of the 79 patients with inhalational anthrax died, although the reliability of the diagnosis in the survivors is questionable.[8] Patients who had onset of disease 30 or more days after release of organisms had a higher reported survival rate compared with those with earlier disease onset. Antibiotics, antianthrax globulin, and vaccine were used to treat some residents in the affected area some time after exposure, but which patients received these interventions and when is not known. In fatal cases, the interval between onset of symptoms and death averaged 3 days. This is similar to the disease course and case fatality rate in untreated experimental monkeys, which have developed rapidly fatal disease even after a latency as long as 58 days.[28]

Modern mortality rates in the setting of contemporary medical and supportive therapy might be lower than those reported historically. However, the 1979 Sverdlovsk experience is not instructive. Although antibiotics, antianthrax globulin, corticosteroids, and mechanical ventilation were used, individual clinical records have not been made public.[8] It is also uncertain if the *B anthracis* strain to which patients were exposed was susceptible to the predominant antibiotics that were used during the outbreak.

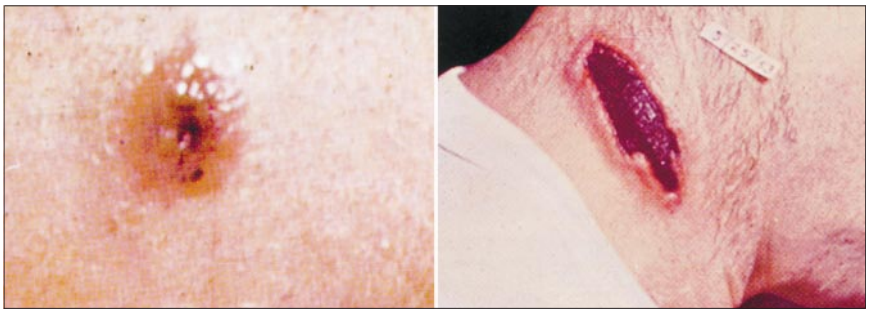
Physiological sequelae of severe anthrax infection in animal models have been described as hypocalcemia, profound hypoglycemia, hyperkalemia, depression and paralysis of respiratory center, hypotension, anoxia, respiratory alkalosis, and terminal acidosis.[44,45] Those animal studies suggest that in addition to the rapid administration of antibiotics, survival might improve with vigilant correction of electrolyte disturbances and acid-base imbalance, glucose infusion, and early mechanical ventilation and vasopressor administration.

Figure 2. Chest Radiograph of a Patient With Inhalational Anthrax



Chest radiograph of a 51-year-old laborer with occupational exposure to airborne anthrax spores taken on day 2 of illness. Lobulated mediastinal widening (arrowheads) is present, consistent with lymphadenopathy, with a small parenchymal infiltrate at the left lung base. Reprinted with permission from Zajtchuk and Bellamy.[23]

Figure 3. Cutaneous Anthrax



Left, Forearm lesion on day 7 of illness shows vesiculation and ulceration of the initial macular or papular anthrax skin lesion. Right, Eschar of the neck on day 15 of illness is typical of the last stage of the lesion before it resolves over 1 to 2 weeks. Reprinted with permission from Binford CH, Connor DH, eds. *Pathology of Tropical and Extraordinary Diseases.* Vol 1. Washington, DC: Armed Forces Institute of Pathology; 1976:119. AFIP negative 71-1290-2.

Cutaneous Anthrax

Cutaneous anthrax occurs following the deposition of the organism into skin with previous cuts or abrasions especially susceptible to infection.[21,46] Areas of exposed skin, such as arms, hands, face, and neck, are the most frequently affected. There are no data to suggest the possibility of a prolonged latency period in cutaneous anthrax. In Sverdlovsk, cutaneous cases occurred only as late as 12 days after the original aerosol release.[8] After the spore germinates in skin tissues, toxin production results in local edema (FIGURE 3). An initially pruritic macule or papule enlarges into a round ulcer by the second day. Subsequently, 1- to 3-mm vesicles may appear, which discharge clear or serosanguinous fluid containing numerous organisms on Gram stain. As shown in Figure 3, development of a painless, depressed, black eschar follows, often associated with extensive local edema. The eschar dries, loosens, and falls off in the next 1 to 2 weeks, most often leaving no permanent scar. Lymphangitis and painful lymphadenopathy can occur with associated systemic symptoms. Although antibiotic therapy does not appear to change the course of eschar formation and heal-

ing, it does decrease the likelihood of systemic disease. Without antibiotic therapy, the mortality rate has been reported to be as high as 20%; with antibiotics, death due to cutaneous anthrax is rare.[2]

Gastrointestinal Anthrax

Gastrointestinal anthrax occurs following deposition and subsequent germination of spores in the upper or lower gastrointestinal tract. The former results in the oral-pharyngeal form of disease.[24-26] An oral or esophageal ulcer leads to development of regional lymphadenopathy, edema, and sepsis.[24-26] The latter results in primary intestinal lesions occurring predominantly in the terminal ileum or cecum,[38] presenting initially with nausea, vomiting, and malaise and progressing rapidly to bloody diarrhea, acute abdomen, or sepsis.[22] Massive ascites has occurred in some cases of gastrointestinal anthrax.[27] Advanced infection may appear similar to the sepsis syndrome occurring in either inhalational or cutaneous anthrax.[2] Some authors suggest that aggressive medical intervention such as would be recommended for inhalational anthrax may reduce mortality, although, given the difficulty of early diagnosis, mortality almost inevitably would be high.[2,22]

DIAGNOSIS

Given the rarity of anthrax infection and the possibility that early cases are a harbinger of a larger epidemic, the first suspicion of an anthrax illness must lead to immediate notification of the local or state health department, local hospital epidemiologist, and local or state health laboratory. By this mechanism, definitive tests can be arranged rapidly through a reference laboratory and, as necessary, the US Army Medical Research Institute of Infectious Diseases (USAMRIID), Fort Detrick, Md.

The first evidence of a clandestine release of anthrax as a biological weapon most likely will be patients seeking medical treatment for symptoms of inhalational anthrax. The sudden appearance of a large number of patients in a city or region with an acute-onset flulike illness and case fatality rates of 80% or more, with nearly half of all deaths occurring within 24 to 48 hours, is highly likely to be anthrax or pneumonic plague (TABLE 1). Currently, there are no effective atmospheric warning systems to detect an aerosol cloud of anthrax spores.[47]

Table 1. Diagnosis of Inhalational Anthrax Infection

Epidemiology	Sudden appearance of multiple cases of severe flulike illness with fulminant course and high mortality
Diagnostic studies	Chest radiograph: widened mediastinum
	Peripheral blood smear: gram-positive bacilli on unspun smear
Microbiology	Blood culture growth of large gram-positive bacilli with preliminary identification of *Bacillus* species
Pathology	Hemorrhagic mediastinitis, hemorrhagic thoracic lymphadenitis, hemorrhagic meningitis

Rapid diagnostic tests for diagnosing anthrax, such as enzyme-linked immunosorbent assay for protective antigen and polymerase chain reaction, are available only at national reference laboratories. Given the limited availability of these tests and the time required to dispatch specimens and perform assays, rapid diagnostic testing would be primarily for confirmation of diagnosis and determining in vitro susceptibility to antibiotics. In addition, these tests will be used in the investigation and management of anthrax hoaxes, such as the series occurring in late 1998.[48] They would also be of value should suspicious materials in the possession of a terrorist be identified as possibly containing anthrax.

If only small numbers of cases present contemporaneously, the clinical similarity of early inhalational anthrax to other acute respiratory tract infections may delay initial diagnosis for some days. However, diagnosis of anthrax could soon become apparent through the astute recognition of an unusual radiological finding, identification in the microbiology laboratory, or recognition of specific pathologic findings. A widened mediastinum on chest radiograph (Figure 2) in a previously healthy patient with evidence of overwhelming flulike illness is essentially pathognomonic of advanced inhalational anthrax and should prompt immediate action.[23,42] Although treatment at this stage would be unlikely to alter the outcome of illness in the patient concerned, it might lead to earlier diagnosis in others.

Microbiologic studies can also demonstrate *B anthracis* and may be the means for initial detection of an outbreak. The bacterial burden may be so great in advanced infection that bacilli are visible on Gram stain of unspun peripheral blood, as has been demonstrated in primate studies (Figure 1). While this is a remarkable finding that would permit an astute clinician or microbiologist to make the diagnosis, the widespread use of automated cell-counter technology in diagnostic laboratories makes this unlikely.[41]

The most useful microbiologic test is the standard blood culture, which should show growth in 6 to 24 hours. If the laboratory has been alerted to the possibility of anthrax, biochemical testing and review of colonial morphology should provide a preliminary diagnosis 12 to 24 hours later. Definitive diagnosis would require an additional 1 to 2 days of testing in all but a few national reference laboratories. It should be noted, however, that if the laboratory has not been alerted to the possibility of anthrax, *B anthracis* may not be correctly identified. Routine laboratory procedures customarily identify a *Bacillus* species from a blood culture approximately 24 hours after growth, but most laboratories do not further identify *Bacillus* species unless specifically requested to do so. In the United States, the isolation of *Bacillus* species most often represents growth of *Bacillus cereus*. The laboratory and clinician must determine whether its isolation represents specimen contamination.[49] There have been no *B anthracis* bloodstream infections reported for more than 20

years. However, given the possibility of anthrax being used as a weapon and the importance of early diagnosis, it would be prudent for laboratory procedures to be modified so that *B anthracis* is excluded after identification of a *Bacillus* species bacteremia.

Sputum culture and Gram stain are unlikely to be diagnostic, given the lack of a pneumonic process.[30] If cutaneous anthrax is suspected, a Gram stain and culture of vesicular fluid will confirm the diagnosis.

A diagnosis of inhalational anthrax also might occur at postmortem examination following a rapid, unexplained terminal illness. Thoracic hemorrhagic necrotizing lymphadenitis and hemorrhagic necrotizing mediastinitis in a previously healthy adult are essentially pathognomonic of inhalational anthrax.[38,43] Hemorrhagic meningitis should also raise strong suspicion of anthrax infection.[23,38,43,50] Despite pathognomonic features of anthrax on gross postmortem examination, the rarity of anthrax makes it unlikely that a pathologist would immediately recognize these findings. If the case were not diagnosed at gross examination, additional days would likely pass before microscopic slides would be available to suggest the disease etiology.

VACCINATION

The US anthrax vaccine, an inactivated cell-free product, was licensed in 1970 and is produced by Bioport Corp, Lansing, Mich (formerly called the Michigan Biologic Products Institute). The vaccine is licensed to be given in a 6-dose series and has recently been mandated for all US military active- and reserve-duty personnel.[51] The vaccine is made from the cell-free filtrate of a nonencapsulated attenuated strain of *B anthracis*.[52] The principal antigen responsible for inducing immunity is the protective antigen.[18,23] A similar vaccine has been shown in 1 small placebo-controlled human trial to be efficacious against cutaneous anthrax.[53] As of March 1, 1999, approximately 590 000 doses of anthrax vaccine have been administered to US Armed Forces (Gary Strawder, Department of Defense, Falls Church, Va, oral communication, April 1999); no serious adverse events have been causally related (Miles Braun, Food and Drug Administration, Rockville, Md, written communication, April 1999). In a study of experimental monkeys, inoculation with this vaccine at 0 and 2 weeks was completely protective against an aerosol challenge at 8 and 38 weeks and 88% effective at 100 weeks.[54]

A human live attenuated vaccine is produced and used in countries of the former Soviet Union.[55] In the Western world, live attenuated vaccines have been considered unsuitable for use in humans.[55]

Current vaccine supplies are limited and the US production capacity is modest. It will be years before increased production efforts can make available sufficient quantities of vaccine for civilian use. However, even if vaccine were available, populationwide vaccination would not be recommended at this time, given the costs and logistics of a large-scale vaccination program and the unlikely occurrence of a bioterrorist attack in any given community. Vaccination of some essential service personnel should be considered if vaccine becomes available. Postexposure vaccination following a biological attack with anthrax would be recommended with antibiotic administration to protect against residual retained spores, if vaccine were available.

THERAPY

Recommendations regarding antibiotic and vaccine use in the setting of a biological anthrax attack are conditioned by a limited number of studies in experimental animals, current understanding of antibiotic resistance patterns, and the possible requirement to treat large numbers of casualties. A number of possible therapeutic strategies have yet to be fully explored experimentally or submitted for approval to the FDA. For these reasons, the working group offers consensus recommendations based on the best available evidence. The recommendations do not represent uses currently approved by the FDA or an official position on the part of any of the federal agencies whose scientists participated in these discussions and will need to be revised as further relevant information becomes available.

Given the rapid course of symptomatic inhalational anthrax, early antibiotic administration is essential. A delay of antibiotic treatment for patients with anthrax infection even by hours may substantially lessen chances for survival.[56,57] Given the difficulty in achieving rapid microbiologic diagnosis of anthrax, all persons with fever or evidence of systemic disease in an area where anthrax cases are occurring should be treated for anthrax until the disease is excluded.

There are no clinical studies of the treatment of inhalational anthrax in humans. Thus, antibiotic regimens commonly recommended for empirical treatment of sepsis have not been studied in this setting. In fact, natural strains of *B anthracis* are resistant to many of the antibiotics used in these empirical regimens, such as those of the extended-spectrum cephalosporins.[58,59] Most naturally occurring anthrax strains are sensitive to penicillin, and penicillin historically has been the preferred therapy for the treatment of anthrax. Penicillin is approved by the FDA for this indication,[41,56,57] as is doxycycline.[60] In studies of small numbers of monkeys infected with susceptible strains of *B anthracis*, oral doxycycline has proved efficacious.[41]

Doxycycline is the preferred option from the tetracycline class of antibiotics because of its proven efficacy in monkey studies and its ease of administration. Other members of this class of antibiotics are suitable alternatives. Although treatment of anthrax infection with ciprofloxacin has not been studied in humans, animal models suggest excellent efficacy.[28,41,61] In vitro data suggest that other fluoroquinolone antibiotics would have equivalent efficacy in treating anthrax infection, although no animal data exist for fluoroquinolones other than ciprofloxacin.[59]

Reports have been published of a *B anthracis* vaccine strain that has been engineered by Russian scientists to resist the tetracycline and penicillin classes of antibiotics.[62] Although the engineering of quinolone-resistant *B anthracis* may also be possible, to date there have been no published accounts of this.

Balancing considerations of efficacy with concerns regarding resistance, the working group recommends that ciprofloxacin or other fluoroquinolone therapy be initiated in adults with presumed inhalational anthrax infection. Antibiotic resistance to penicillin- and tetracycline-class antibiotics should be assumed following a terrorist attack until laboratory testing demonstrates otherwise. Once the antibiotic susceptibility of the *B anthracis* strain of the index case has been determined, the most widely available, efficacious, and least toxic antibiotic should be administered to patients and persons requiring postexposure prophylaxis.

In a contained casualty setting (a situation in which a modest number of patients require therapy), the working group recommends intravenous antibiotic therapy, as shown in TABLE 2. If the number of persons requiring therapy is sufficiently high (ie, a mass casualty setting), the working group recognizes that intravenous therapy will no longer be possible for reasons of logistics and/or exhaustion of equipment and antibiotic supplies, and oral therapy will need to be used (TABLE 3). The threshold number of cases at which parenteral therapy becomes impossible depends on a variety of factors, including local and regional health care resources.

In experimental animals, antibiotic therapy during anthrax infection has prevented development of an immune response.[28,62] This suggests that even if the antibiotic-treated patient survives anthrax infection, risk for recurrence remains for at least 60 days because of the possibility of delayed germination of spores. Therefore, the working group recommends that antibiotic therapy be continued for 60 days, with oral therapy replacing intravenous therapy as soon as a patient's clinical condition improves. If vaccine were to become widely available, postexposure vaccination in patients being treated for anthrax infection might permit the duration of antibiotic administration to be shortened to 30 to 45 days, with concomitant administration of 3 doses of anthrax vaccine at 0, 2, and 4 weeks.

The treatment of cutaneous anthrax historically has been with oral penicillin. The working group recommends that oral fluoroquinolone or tetracycline antibiotics as well as amoxicillin in the adult dosage schedules described in Tables 2 and 3 would be suitable alternatives if antibiotic susceptibility is proved. Although previous guidelines have suggested treating cutaneous anthrax for 7 to 10 days,[23,49] the working group recommends treatment for 60 days in the setting of bioterrorism, given the presumed exposure to the primary aerosol. Treatment of cutaneous anthrax generally prevents progression to systemic disease, although it does not prevent the formation and evolution of the eschar. Topical therapy is not useful.[2]

Other antibiotics effective against *B anthracis* in vitro include chloramphenicol, erythromycin, clindamycin, extended-spectrum penicillins, macrolides, aminoglycosides, vancomycin hydrochloride, cefazolin, and other first-generation cephalosporins.[58,59,64] The efficacy of these antibiotics has not been tested in humans or animal studies. The working group recommends the use of these antibiotics only if the previously cited antibiotics are unavailable or if the strain is otherwise antibiotic resistant. Natural resistance of *B anthracis* strains exists against sulfamethoxazole, trimethoprim, cefuroxime, cefotaxime sodium, aztreonam, and ceftazidime.[58,59,64] Therefore, these antibiotics should not be used in the treatment or prophylaxis of anthrax infection.

Postexposure Prophylaxis

Guidelines regarding which populations would require postexposure prophylaxis following the release of anthrax as a biological weapon would need to be developed quickly by state and local health departments in consultation with national experts. These decisions require estimates of the timing and location of the exposure and the relevant weather conditions in an outdoor release.[65] Ongoing monitoring of cases would be needed to define the

Table 2. Working Group Recommendations for Medical Therapy for Patients With Clinically Evident Inhalational Anthrax Infection in the Contained Casualty Setting[28,41,60,62,63]*

	Initial Therapy†	Optimal Therapy if Strain Is Proven Susceptible	Duration, d‡
Adults	Ciprofloxacin, 400 mg intravenously every 12 h	Penicillin G, 4 million U intravenously every 4 h Doxycycline, 100 mg intravenously every 12 h§	60
Children‖	Ciprofloxacin, 20-30 mg/kg per day intravenously divided into 2 daily doses, not to exceed 1 g/d	Age <12 y: penicillin G, 50 000 U/kg intravenously every 6 h Age ≥12 y: penicillin G, 4 million U intravenously every 4 h	60
Pregnant women¶	Same as for nonpregnant adults		
Immunosuppressed persons	Same as for nonimmunosuppressed adults and children		

*Most recommendations are based on animal studies or in vitro studies and are not approved by the US Food and Drug Administration (FDA). These recommendations are not FDA approved but were reached by consensus of the working group. See text for explanations and alternatives.
†In vitro studies suggest ofloxacin, 400 mg intravenously every 12 hours, or levofloxacin, 500 mg intravenously every 24 hours, could be substituted for ciprofloxacin.
‡Oral antibiotics should be substituted for intravenous antibiotics as soon as clinical condition improves.
§In vitro studies suggest tetracycline could be substituted for doxycycline.
‖Doxycycline could also be used. For children heavier than 45 kg, use adult dosage. For children 45 kg or lighter, use 2.5 mg/kg doxycycline intravenously every 12 hours. Refer to management of pediatric population in text for details.
¶Refer to section on management of pregnant women in text for details.

high-risk areas, direct follow-up, and guide the addition or deletion of groups to receive postexposure prophylaxis.

There are no FDA-approved postexposure antibiotic regimens following exposure to an anthrax aerosol. For postexposure prophylaxis, the working group recommends the same antibiotic regimen as that recommended for treatment of mass casualties; prophylaxis should be continued for 60 days (Table 3).

Management of Special Groups

Consensus recommendations for special groups as set forth herein reflect the clinical and evidence-based judgments of the working group and at this time do not necessarily correspond with FDA-approved use, indications, or labeling.

Children. It has been recommended that ciprofloxacin and other fluoroquinolones should not be used in children younger than 16 to 18 years because of a link to permanent arthropathy in adolescent animals and transient arthropathy in a small number of children.[60] However, balancing these risks against the risks of anthrax caused by an engineered antibiotic-resistant strain, the working group recommends that ciprofloxacin be used in the pediatric population for initial therapy or postexposure prophylaxis following an anthrax attack (Table 2). If antibiotic susceptibility testing allows, penicillin should be substituted for the fluoroquinolone.

As a third alternative, doxycycline could be used. The American Academy of Pediatrics has recommended that doxycycline not be used in children younger than 9 years because the drug has resulted in retarded skeletal growth in infants and discolored teeth in infants and children.[60] However, the serious risk of infection following an anthrax attack supports the consensus recommendation that doxycycline be used in children if antibiotic susceptibility testing, exhaustion of drug supplies, or allergic reaction preclude use of penicillin and ciprofloxacin.

In a contained casualty setting, the working group recommends that children receive intravenous antibiotics (Table 2). In a mass casualty setting and as postexposure prophylaxis, the working group recommends that children receive oral antibiotics (Table 3).

The US vaccine is licensed for use only in persons aged 18 to 65 years because studies to date have been conducted exclusively in this group.[52] No data exist for children, but based on experience with other inactivated vaccines, it is likely that the vaccine would be safe and effective.

Pregnant Women. Fluoroquinolones are not generally recommended during pregnancy because of their known association with arthropathy in adolescent animals and small numbers of children. Animal studies have discovered no evidence of teratogenicity related to ciprofloxacin, but no controlled studies of ciprofloxacin in pregnant women have been conducted. Balancing these possible risks against the concerns of anthrax due to engineered antibiotic-resistant strains, the working group recommends that ciprofloxacin be used in pregnant women for therapy and postexposure prophylaxis following an anthrax attack (Tables 2 and 3). No adequate controlled trials of penicillin or amoxicillin administration during pregnancy exist. However, the CDC recommends penicillin for the treatment of syphilis during pregnancy and amoxicillin as a treatment alternative for chlamydial infections during pregnancy.[60]

The working group recommends that pregnant women receive fluoroquinolones in the usual adult dosages. If susceptibility testing allows, intravenous penicillin in the usual adult dosages should be substituted for fluoroquinolones. As a third alternative, intravenous doxycycline could be used. The tetracycline class of antibiotics has been associated with both toxic effects in the liver in pregnant women and fetal toxic effects, including retarded skeletal growth.[60] Balancing the risks of anthrax infection with those associated with doxycycline use in pregnancy, the working group recommends that doxycycline be used in pregnant women for therapy and postexposure prophylaxis if antibiotic susceptibility testing, exhaustion of drug supplies, or allergic sensitivity preclude the use of penicillin and ciprofloxacin. If doxycycline is used in pregnant women, periodic liver function testing should be performed if possible.

Table 3. Working Group Recommendations for Medical Therapy for Patients With Clinically Evident Anthrax Infection in the Mass Casualty Setting or for Postexposure Prophylaxis[41]*

	Initial Therapy†	Optimal Therapy if Strain Is Proven Susceptible	Duration, d
Adults	Ciprofloxacin, 500 mg by mouth every 12 h	Amoxicillin, 500 mg every 8 h Doxycycline, 100 mg by mouth every 12 h‡	60
Children§	Ciprofloxacin, 20-30 mg/kg per day by mouth divided into 2 daily doses, not to exceed 1 g/d	Weight ≥20 kg: amoxicillin, 500 mg by mouth every 8 h Weight <20 kg: amoxicillin, 40 mg/kg divided into 3 doses to be taken every 8 h	60
Pregnant women‖	Ciprofloxacin, 500 mg by mouth every 12 h	Amoxicillin, 500 mg by mouth every 8 h	60
Immunosuppressed persons	Same as for nonimmunosuppressed adults and children		

*Most recommendations are based on animal studies or in vitro studies and are not approved by the US Food and Drug Administration (FDA). These recommendations are not FDA approved but were reached by consensus of the working group. See text for explanations and alternatives.
†In vitro studies suggest ofloxacin, 400 mg by mouth every 12 hours, or levofloxacin, 500 mg by mouth every 24 hours, could be substituted for ciprofloxacin.
‡In vitro studies suggest tetracycline, 500 mg by mouth every 6 hours, could be substituted for doxycycline.
§Doxycycline could also be used. For children heavier than 45 kg, use adult dosage. For children 45 kg or lighter, use 2.5 mg/kg doxycycline by mouth every 12 hours. Refer to management of pediatric population in text for details.
‖Refer to management of pregnant population in text for details.

Ciprofloxacin (and other fluoroquinolones), penicillin, and doxycycline (and other tetracyclines) are each excreted in breast milk. Therefore, a breast-feeding woman should be treated or given prophylaxis with the same antibiotic as her infant based on what is most safe and effective for the infant (see pediatric guidelines herein) to minimize risk to the infant.

Immunosuppressed Persons. The antibiotic treatment or postexposure prophylaxis for anthrax among those who are immunosuppressed has not been studied in human or animal models of anthrax infection. Therefore, the working group consensus recommendation is to administer antibiotics as for immunocompetent adults and children (Tables 2 and 3).

INFECTION CONTROL

There are no data to suggest patient-to-patient transmission of anthrax occurs.[8,46] Thus, standard barrier isolation precautions are recommended for hospitalized patients with all forms of anthrax infection, but the use of high-efficiency particulate air filter masks or other measures for airborne protection are not indicated.[66] There is no need to immunize or provide prophylaxis to patient contacts (eg, household contacts, friends, coworkers) unless a determination is made that they, like the patient, were exposed to the aerosol at the time of the attack.

In addition to immediate notification of the hospital epidemiologist and state health department, the local hospital microbiology laboratories should be notified at the first indication of anthrax so that safe specimen processing under biosafety level 2 conditions can be undertaken.[41,67] A number of disinfectants used for standard hospital infection control, such as hypochlorite, are effective in cleaning environmental surfaces contaminated with infected bodily fluids.[17,66]

Proper burial or cremation of humans and animals who have died because of anthrax infection is important in preventing further transmission of the disease. Serious consideration should be given to cremation. Embalming of bodies could be associated with special risks.[66] If autopsies are performed, all related instruments and materials should be autoclaved or incinerated.[66] Animal transmission might occur if infected animal remains are not cremated or buried.[16,21]

Figure 4. Day of Onset of Inhalational Anthrax Following Sverdlovsk Accident

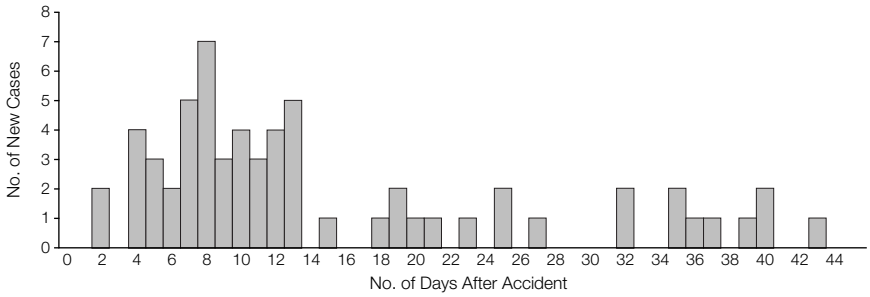


Figure is based on data from Guillermin.[68]

DECONTAMINATION

Recommendations regarding decontamination in the event of an intentional aerosolization of anthrax spores are based on evidence concerning aerosolization, anthrax spore survival, and environmental exposures at Sverdlovsk and among goat hair mill workers. The greatest risk to human health following an intentional aerosolization of anthrax spores occurs during the period in which anthrax spores remain airborne, called *primary aerosolization*. The duration for which spores remain airborne and the distance spores travel before they become noninfectious or fall to the ground is dependent on meteorological conditions and aerobiological properties of the dispersed aerosol.[8,65] Under circumstances of maximum survival and persistence, the aerosol would be fully dispersed within hours to 1 day at most, well before the first symptomatic cases would be seen. Following the discovery that a bioweapon has been used, anthrax spores may be detected on environmental surfaces using rapid assay kits or culture, but they provide no indication as to the risk of reaerosolization.

The risk that anthrax spores might pose to public health after the period of primary aerosolization can be inferred from the Sverdlovsk experience, investigations in animal hair processing plants, and modeling analyses by the US Army. At Sverdlovsk, new cases of inhalational anthrax developed as late as 43 days after the presumed date of release, but none occurred during the months and years afterward.[68] Some have questioned whether any of those cases with onset of disease beyond 7 days might have represented illness following resuspension of spores from the ground or other surfaces, a process that has been called *secondary aerosolization*. While it is impossible to state with certainty that secondary aerosolizations did not occur, it appears unlikely. It should be noted that few efforts were made to decontaminate the environment after the accident and only 47 000 of the city's 1 million inhabitants were vaccinated.[8] The epidemic curve (FIGURE 4) is typical for a common-source epidemic, and it is possible to account for virtually all patients having been within the area of the plume on the day of the accident. Moreover, if secondary aerosolization had been important, new cases almost certainly would have continued for a period well beyond the observed 43 days.

Although persons working with animal hair or hides are known to be at increased risk of developing inhalational or cutaneous anthrax, surprisingly few of those exposed in the United States have developed disease. During the first half of this century, a significant number of goat hair mill workers were likely exposed to aerosolized spores. Mandatory vaccination became a requirement

for working in goat hair mills only in the 1960s. Meanwhile, many unvaccinated person-years of high-risk exposure had occurred, but only 13 cases of inhalational anthrax were reported.[19,44] One study of environmental exposure was conducted at a Pennsylvania goat hair mill at which workers were shown to inhale up to 510 *B anthracis* particles of at least 5 µm in diameter per person per 8-hour shift. These concentrations of spores were constantly present in the environment during the time of this study,[44] but no cases of inhalational anthrax occurred.

Modeling analyses have been carried out by US Army scientists seeking to determine the risk of secondary aerosolization. One study concluded that there was no significant threat to personnel in areas contaminated by 1 million spores per square meter either from traffic on asphalt-paved roads or from a runway used by helicopters or jet aircraft.[69] A separate study showed that in areas of ground contaminated with 20 million *Bacillus subtilis* spores per square meter, a soldier exercising actively for a 3-hour period would inhale between 1000 and 15 000 spores.[70]

Much has been written about the technical difficulty of decontaminating an environment contaminated with anthrax spores. A classic case is the experience at Gruinard Island in the United Kingdom. During World War II, British military undertook explosives testing with anthrax spores on this island off the Scottish coast. Spores persisted and remained viable for 36 years following the conclusion of testing. Decontamination of the island occurred in stages, beginning in 1979 and ending in 1987, when the island was finally declared fully decontaminated. The total cost is unpublished, but materials required included 280 tons of formaldehyde and 2000 tons of seawater.[17,71]

If an environmental surface is proved to be heavily contaminated with anthrax spores in the immediate area of a spill or close proximity to the point of release of an anthrax aerosol, decontamination of that area may decrease the slight risk of acquiring anthrax by secondary aerosolization. However, decontamination of large urban areas or even a building following an exposure to an anthrax aerosol would be extremely difficult and is not indicated. Although the risk of disease caused by secondary aerosolization would be extremely low, it would be difficult to offer absolute assurance that there was not risk whatsoever. Postexposure vaccination, if vaccine were available, might be a possible intervention that could further lower the risk of anthrax infection in this setting.

In the setting of an announced alleged anthrax release, such as the series of anthrax hoaxes occurring in many areas of the United States in 1998,[48] any person coming in direct physical contact with a substance alleged to be anthrax should perform thorough washing of the exposed skin and articles of clothing with soap and water.[72] Further decontamination of directly exposed individuals or of others is not indicated. In addition, any person in direct physical contact with the alleged substance should receive postexposure antibiotic prophylaxis until the substance is proved not to be anthrax. If the alleged substance is proved to be anthrax, immediate consultation with experts at the CDC and USAMRIID should be obtained.

ADDITIONAL RESEARCH

To develop a maximally effective response to a bioterrorist incident involving anthrax, the medical community will require new knowledge of the organism, its genetics and pathogenesis, improved rapid diagnostic techniques, improved prophylactic and therapeutic regimens, and an improved second-generation vaccine.[47] A recently published Russian study indicates that genes transferred from the related *B cereus* can act to enable *B anthracis* to evade the protective effect of the live attenuated Russian vaccine in a rodent model.[73] Research is needed to determine the role of these genes with respect to virulence and ability to evade vaccine-induced immunity. Furthermore, the relevance of this finding for the US vaccine needs to be established. An accelerated vaccine development effort is needed to allow the manufacture of an improved second-generation product that requires fewer doses. Finally, an expanded knowledge base is needed regarding possible maximum incubation times after inhalation of spore-containing aerosols and optimal postexposure antibiotic regimens.

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Disclaimers: In many cases, the indication and dosages and other information are not consistent with current approved labeling by the US Food and Drug Administration (FDA). The recommendations on the use of drugs and vaccine for uses not approved by the FDA do not represent the official views of the FDA or of any of the federal agencies whose scientists participated in these discussions. Unlabeled uses of the products recommended are noted in the sections of this article in which these products are discussed. Where unlabeled uses are indicated, information used as the basis for the recommendation is discussed.

The views, opinions, assertions, and findings contained herein are those of the authors and should not be construed as official US Department of Defense or US Department of Army positions, policies, or decisions unless so designated by other documentation.

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RESEARCH LETTER

NIH Research Grants: Funding and Re-funding

To the Editor: National Institutes of Health (NIH) grants play an important role in the careers of the research faculty in medical schools. Given the importance of NIH funding in an academic career, we sought to determine several aspects of NIH funding that have, to the best of our knowledge, not been examined in detail. These are (1) the median length of time of NIH funding during the academic life of an individual, (2) the predictive value, for long-term funding, of receiving NIH funding at any given time, and (3) the effect of length of the unfunded period on the likelihood that an investigator will be subsequently funded.

Methods. We obtained the funding histories of individuals who were awarded any NIH grants in the index years 1972 and 1982, and tracked individual funding histories for 25 years and 15 years, respectively. Data consisted of the number of grants each individual received annually following the index year. A total of 1707 individuals received awards in 1972 and 1639 in 1982. Because of the nature of record keeping at the NIH, the precise length of each award was not available. Based on the historical experience of NIH funding, we assumed that the average length of an NIH award is 4 years.

Results. The mean number of awards obtained by individuals throughout their careers was 2.5 for the 1972 and 3.3 for the 1982 cohort; the median for both groups was 2.0. About 40% of individuals who obtain an NIH grant never received another for the rest of their careers.

The best predictor of future funding appears to be the number of grants garnered during a 10-year period. Thus, for both the 1972 and 1982 cohorts, we computed the proportion of individuals obtaining l, 2, or more than 2 awards over a 10-year period from 1972 to 1981 or 1982 to 1991, respectively. The distribution of the individuals into these 3 categories was similar in the 2 cohorts: 39.0% vs 35.0%, 18.3% vs 22.0%, and 42.4% vs 42.0%, respectively. For individuals who only obtained 1 grant for the 10-year period (1972-1981 or 1982-1991), 92.5% and 93%, respectively, did not obtain any funding for the subsequent period until 1997. Of those who received 1 additional grant (or a total of 2 grants for the 10-year period), 72% did not obtain any subsequent funding until 1997. These 2 cohorts were in contrast with those who obtained more than 2 grants for the 10-year interval. Only 27% of these individuals failed to obtain a grant for the subsequent period.

Comment. The cumulative period of NIH funding appears to be rather brief for most individuals. Neither the possession of an NIH grant nor the apparent ability to acquire one based on prior research training or history predicts whether an individual will receive future grants.

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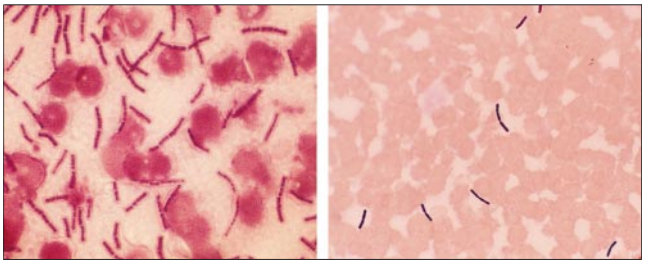
CORRECTIONS

Incorrect Equation: In the Original Contribution entitled "Empirical Evidence of Design-Related Bias in Studies of Diagnostic Tests" published in the September 15, 1999, issue of THE JOURNAL (1999;282:1061-1066), the equation was incorrect. On page 1063, the equation should have appeared:

$$\text{DOR} = \frac{\text{Sensitivity}}{(1 - \text{Sensitivity})} \div \frac{(1 - \text{Specificity})}{\text{Specificity}}$$

Incorrect Color Reproduction: In the Consensus Statement entitled "Anthrax as a Biological Weapon: Medical and Public Health Management" published in the May 12, 1999, issue of THE JOURNAL (1999;281:1735-1745), the color of the photomicrograph in Figure 1 on page 1727 was incorrectly reproduced. The correct image showing gram-positive anthrax bacilli in a peripheral blood smear from a rhesus monkey that died of inhalational anthrax is shown below, left. A second photomicrograph (lower magnification) of a gram stain of the peripheral blood of a rhesus monkey that died of inhalational anthrax is also shown below, right.

Figure. Gram Stains of *Bacillus anthracis*



Left, Reprinted with permission from Zajtchuk R, Bellamy RF, eds. *Textbook of Military Medicine: Medical Aspects of Chemical and Biological Warfare*. Washington, DC: Office of the Surgeon General, US Dept of the Army; 1997.

- All patients should be treated with anthrax vaccine if available; antibiotic treatment should be continued until 3 doses of vaccine have been administered (day 0, 14 and 28). If vaccine is unavailable, antibiotic treatment should be continued for 60 days.

Prophylaxis:

- If vaccine is available, all exposed persons (as determined by local and state health depts) should be vaccinated with 3 doses of anthrax vaccine (days 0, 14 and 28)
- Start antibiotic prophylaxis immediately after exposure with ciprofloxicin (500 mg po q 12 hrs) or doxycycline (100 mg po q 12 hrs). (If strain is penicillin-susceptible, therapy can be modified to penicillin or amoxicillin.)
- Antibiotic prophylaxis should be continued until 3 doses of vaccine have been administered; if vaccine is unavailable, antibiotics should be continued for 60 days.

PLACER COUNTY
HEALTH AND HUMAN SERVICES
COMMUNICABLE DISEASE CONTROL

Medical Treatment and Response to Suspected Anthrax: Information for Health Care Providers During Biologic Emergencies

ALL SUSPECT CASES OF ANTHRAX MUST BE REPORTED IMMEDIATELY TO THE PLACER COUNTY HEALTH AND HUMAN SERVICES, COMMUNICABLE DISEASE CONTROL:

During Business Hours: (530) 889-7141

After Hours (Nights, Weekends and Holidays): Health Officer Richard J. Burton, M.D., M.P.H., at (530) 889-7119

(In the event that you are unable to reach a Communicable Disease Control Contact, please call the Placer County Office of Emergency Services at (530) 886-5300 or the 24-hour dispatch at (530) 886-5375).

I. KEY SUMMARY POINTS

- Anthrax can be transmitted by inhalation, ingestion, or inoculation (inhalation is the most likely during a bioterrorist attack)
- The spore form of anthrax is highly resistant to physical and chemical agents; spores can persist in the environment for years
- **Anthrax is <u>not</u> transmitted from person to person**

Clinical:

- Incubation period is 1-5 days (range up to 43 days)
- Inhalation anthrax presents as acute hemorrhagic mediastinitis
- Biphasic illness, with initial phase characterized by nonspecific flu-like illness followed by acute phase characterized by acute respiratory distress and toxemia (sepsis)
- Chest x-ray findings: **Mediastinal widening in a previously healthy patient in the absence of trauma is pathognomonic for anthrax**
- Mortality rate for inhalation anthrax approaches 90%, even with treatment. Shock and death within 24 – 36 hours

Laboratory Diagnosis:

- Laboratory specimens should be handled in a Biosafety Level 2 facility (e.g. California state Microbial Diseases Laboratory, Placer County Public Health Laboratory)
- Gram stain shows gram positive bacilli, occurring singly or in short chains, often with squared off ends (safety pin appearance). In advanced disease, a gram stain of unspun blood may be positive
- Distinguishing characteristics on culture include: non-hemolytic, non-motile, capsulated bacteria that are susceptible to gamma phage lysis
- ELISA and PCR tests are available at national reference laboratories

Patient Isolation:

- Standard barrier isolation precautions. Patients do <u>not</u> require isolation rooms
- **Anthrax is <u>not</u> transmitted person to person**

Treatment:

- Prompt initiation of antibiotic therapy is essential

- Antibiotic susceptibility testing is KEY to guiding treatment
- Ciprofloxicin (400 mg IV q 12 hr) is the antibiotic of choice for penicillin-resistant anthrax or for empiric therapy while awaiting susceptibility results
- All patients should be treated with anthrax vaccine if available; antibiotic treatment should be continued until 3 doses of vaccine have been administered (day 0, 14 and 28). If vaccine is unavailable, antibiotic treatment should be continued for 60 days.

Prophylaxis:

- If vaccine is available, all exposed persons (as determined by local and state health depts) should be vaccinated with 3 doses of anthrax vaccine (days 0, 14 and 28)
- Start antibiotic prophylaxis immediately after exposure with ciprofloxicin (500 mg po q 12 hrs) or doxycycline (100 mg po q 12 hrs). (If strain is penicillin-susceptible, therapy can be modified to penicillin or amoxicillin.)
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II. Introduction/Epidemiology

Anthrax is a disease caused by *Bacillus anthracis* which can infect most warm-blooded animals, including man. Transmission to humans usually occurs through contact with infected animals or contaminated animal products. Humans become infected by inoculation, inhalation, or ingestion of the bacterium. In humans, naturally-occurring

anthrax primarily involves the skin or rarely, the lungs or the gastrointestinal tract. **The bacillus produces a resistant spore which could be dispersed as a small particle aerosol. In the event of a biologic terrorist attack, aerosolization is the most likely mode of transmission, and inhalational anthrax would be the predominant form of disease affecting persons exposed to the aerosol**.

The spore form of *B. anthracis* is highly resistant to physical and chemical agents. The organism has been shown to persist for years in factories contaminated during the processing of infected animal products. Soil, animal feed, and to a lesser extent, ground water are the major reservoirs for anthrax.

Although human anthrax is infrequent and sporadic in the United States and most other industrialized countries, human cases (primarily cutaneous) continue to be reported from Africa, Asia, Europe, and the Americas. Although anthrax-contaminated soil exists in many foci throughout the United States, the number of cases reported annually has declined throughout the last five decades; five human cases (all cutaneous anthrax) were reported between 1981-1996. **A suspected case of anthrax in a patient *without* a clear exposure history (e.g., a traveler returning from an area with known animal cases or a person with exposure to imported animal hides) may be the first clue of a bioterrorist attack. Therefore, even a single, suspect case should prompt immediate notification of the Placer County Health and Human Services, Communicable Disease Control, (Business hours: (530) 889-7141; After hours: Health Officer Richard J. Burton, M.D., M.P.H., at (530) 889-7119)**

Person to person transmission of anthrax is extremely rare.

III. Significance as a Potential Bioterrorist Agent

- Anthrax has been weaponized by many countries during the last 50 years, including the United States (during the 1950's) and Iraq during the Gulf War.
- Anthrax is easy to cultivate and spores are readily produced.
- Anthrax spores are highly resistant to heat and disinfection.

- If aerosolized spores are inhaled, a severe hemorrhagic mediastinitis can occur with mortality rates approaching 90% even with appropriate treatment.

- Currently, anthrax vaccine is in limited supply in the United States and not available to the general public.

IV. Clinical Manifestations

During an act of bioterrorism, release of an aerosol will be the most likely route of transmission. Given this, most exposed individuals will present with symptoms of inhalation anthrax with only a few, if any, presenting with the cutaneous form of the disease. Gastrointestinal anthrax would be much less likely.

Inhalation Anthrax presents as acute hemorrhagic mediastinitis after inhalation of airborne particles contaminated with *B. anthracis* spores. Inhalation anthrax does **not** present as an acute pneumonia.

Incubation period - illness usually occurs within 1-5 days of exposure (may be as long as 43 days)

Symptoms - Typically biphasic illness

Initial Phase is characterized by flu-like symptoms:

mild, nonspecific respiratory illness
malaise, fatigue, myalgia
low-grade fever
nonproductive cough
mild chest discomfort (occasionally)
rhonchi may be heard, exam otherwise normal

Acute Phase develops after 2-5 days, it may be briefly preceded by 1-2 days of improvement. Characteristic findings include:

acute severe respiratory distress
dyspnea, cyanosis, stridor and profuse diaphoresis
subcutaneous edema of chest and neck

markedly elevated temperature, pulse, respiratory rate
moist crepitant rales

x-ray findings: **mediastinal widening in an otherwise healthy persons is a pathognomonic sign**; pleural effusion may be present, evidence of pneumonia is often lacking

Shock develops rapidly, sometimes accompanied by evidence of hemorrhagic meningitis, and patients usually die within 24 hours of onset of the acute phase. In prior outbreaks, mortality rates approached 90% despite appropriate antibiotic therapy.

The differential diagnosis of acute mediastinitis includes: esophageal perforation; trauma; contiguous spread from a head, neck or thoracic infection; and post-surgical infections after cardiothoracic procedures. **Anthrax should be strongly considered in any previously healthy patient with acute mediastinitis.**

The diagnosis of inhalation anthrax requires a very high index of suspicion, most often based on epidemiologic evidence of a potential exposure. In the initial stages after a bioterrorist attack, a recognized source of exposure would likely be absent -- clinical suspicion is of utmost importance.

Cutaneous Anthrax: presents as a "malignant pustule or malignant carbuncle" resulting from introduction of the anthrax bacillus beneath the skin by inoculation or contamination of a pre-existent break in the skin.

Incubation period - ranges from 1-7 days but is commonly 2-5 days

Symptoms - an evolving skin lesion, usually located on the exposed parts of the body (face, neck, arms), with a varying degree of associated edema. The skin lesion typically progresses as follows:

Small, painless, pruritic papule **>>>** small ring of vesicles that coalesce into a single large vesicle **>>>** vesicle ruptures to form depressed ulcer **>>>** 1-3 cm eschar develops in center (7-10 days from onset of lesion) **>>>** eschar falls off (after 1-2 weeks) leaving a permanent scar.

Systemic symptoms including fever, headache, myalgias, and regional lymphangitis/lymphadenopathy have been described. Lesions on the face and neck may be associated with significant edema and impingement of the trachea from neck swelling can occur. "Malignant edema" describes a syndrome with marked edema, induration and multiple bullae at the site of inoculation associated with generalized toxemia. Septicemia is rare. Untreated cutaneous anthrax has a case fatality rate up to 20%, but fatalities are rare (< 1%) with effective antibiotic treatment.

Gastrointestinal Anthrax: occurs after the ingestion of contaminated food, particularly raw or undercooked meat from infected animals.

Incubation period - ranges from 2-7 days

Symptoms - Two clinical presentations, *intestinal* and *oropharyngeal*, have been described. The symptoms of intestinal anthrax are initially nonspecific and include nausea, vomiting, anorexia and fever. As the disease progresses, abdominal pain, hematemesis and bloody diarrhea develop, occasionally accompanied by ascites. The patient may present with the findings of an acute surgical abdomen. Oropharyngeal anthrax is associated with cervical edema and necrosis. A lesion, resembling a cutaneous anthrax lesion, may be seen in the oral cavity on the posterior wall, the hard palate or the tonsils. Patients typically complain of fever, dysphagia and lymphadenopathy. Toxemia, shock and cyanosis characterize the terminal stages of both forms of the disease. The case fatality rate for gastrointestinal anthrax ranges from 25 to 60%.

Meningitis: Meningitis occurs in less than 5% of cases, and may be a complication of any form of anthrax (inhalational, gastrointestinal or cutaneous). Rarely does it occur without a primary focus. It is usually hemorrhagic.

Incubation period - concurrent with or one to several days after the onset of cutaneous, inhalation or gastrointestinal anthrax.

Symptoms - abrupt onset of meningeal symptoms including nausea, vomiting, myalgia, chills and dizziness. Laboratory findings are notable for a hemorrhagic meningitis. Encephalomyelitis and cortical hemorrhages have been reported; death occurs in 1-6 days.

V. **Laboratory Diagnosis**

Laboratory work with clinical specimens must be done under Biosafety Level 2 conditions. If infection with *Bacillus anthracis* is suspected, please *immediately* call the Placer County Health and Human Services, Communicable Disease Control at (530) 889-7141 arrange for submission of specimens to an appropriate reference laboratory for confirmatory testing. After hours call Placer County Health Officer Richard J. Burton, M.D., M.P.H., at (530) 889-7119.

- **Culture** is the definitive test for anthrax.

  Bacillus anthracis can be isolated from blood, pleural fluid, CSF, ascitic fluid, vesicular fluid or lesion exudate. Sputum cultures are rarely positive. When culturing a lesion, collect either vesicular fluid or exudate from the ulcer. If there is no visible exudate, lift the edge of the eschar with a pair of forceps and collect the fluid near the edge.

  Blood cultures may be positive for bacterial growth in 12-48 hours using standard technology; however, the ability of most clinical microbiology laboratories to definitively identify *B. anthracis* may be limited.

- **Microscopy**

  - **Gram stain**

    - Gram stain should be performed on vesicular fluid or exudate from ulcerative lesions for suspected cutaneous anthrax, pleural fluid for suspected inhalation anthrax, and CSF for suspected meningeal anthrax. **In advanced disease, a gram stain of unspun blood may be positive.** The Gram stain shows gram positive bacilli, usually occurring singly or in short chains, often with squared-off ends (safety-pin appearance).

  - **Direct Fluorescent Antibody (DFA) Test**

        - Rapid diagnostic staining technique. This test has been used to examine exudate from cutaneous lesions, CSF and tissue. Not generally helpful for inhalation anthrax because respiratory/pleural fluid specimens are usually negative in the early stages of disease when rapid diagnosis is most critical. Contact the Placer County Public Health Laboratory at (530) 889-7205 for assistance.

    - **Rapid diagnostic tests**

        - An ELISA assay for protective antigen detection and PCR for detection of nucleic acid can provide a preliminary diagnosis of anthrax within several hours. Currently, these tests are only available at reference laboratories.

- ***Evaluation of a Blood Culture that is Suspicious for Anthrax:*** **The following steps are needed to presumptively identify anthrax in the microbiology laboratory:**

    - Overnight incubation on a blood or nutrient agar isolation plate
    - Gram stain shows large gram positive rods with square or concave ends
    - Blood agar colonies are non-hemolytic, rough, gray-white, tenacious colonies with comma- shaped protrusions
    - Subculture to blood agar plates to test for lysis with gamma phage and penicillin susceptibility. (**NOTE: Although naturally-occurring anthrax is penicillin-sensitive, in the event of a bioterrorist event, an anthrax strain resistant to penicillin may have been released.**)
    - Test for lack of growth on phenylethyl alcohol blood agar, lack of gelatin hydrolysis, and lack of salicin fermentation
    - The bacterial capsule can be demonstrated on nutrient agar containing 0.7% sodium bicarbonate incubated overnight in a candle jar. Examine for capsule with methylene blue or India ink.

To distinguish *Bacillus anthracis* from other *Bacillus species:* Distinguishing features include that *Bacillus anthracis* is non-hemolytic, non-motile, capsulated and susceptible to gamma phage lysis.

Summary: *Bacillus anthracis* is a gram positive bacillus that is white or gray in color, nonhemolytic or weakly so, nonmotile, gamma phage and usually penicillin susceptible, and able to produce the characteristic capsule.

- **Serology** - not helpful for rapidly establishing the diagnosis during the acute illness.

- **Autopsy Findings** - identifying thoracic hemorrhagic necrotizing lymphadenitis and hemorrhagic necrotizing mediastinitis in a previously healthy patient is essentially pathognomonic for inhalation anthrax. Hemorrhagic meningitis would also be a distinct clue to the diagnosis of anthrax.

****NOTE: In the event of a bioterrorist event, the anthrax strain may be penicillin resistant. There are currently no NCCLS standards for susceptibility testing for *B. anthracis*. Microbiology laboratories must alert the Placer County Public Health Laboratory (530-889-7205, after hours 530-889-7119) as soon as *B. anthracis* is identified so that susceptibility testing at a national reference laboratory can be arranged. The results of susceptibility testing are crucial in guiding both therapy and prophylaxis for potentially infected persons.**

VI. Handling Laboratory Specimens

Biosafety Level 2 practices, containment equipment and facilities are recommended for procedures on clinical materials suspected as being positive for anthrax. Laboratory staff handling specimens from persons who might have anthrax must wear surgical gloves, protective gowns and shoe covers. Laboratory tests should be performed in Biological Safety Level 2 cabinets and blood cultures should be maintained in a closed system. Every effort should be made to avoid splashing or creating an aerosol, and protective eye wear and masks should be worn if work cannot be done in a Biological Safety Level 2 cabinet. A full-face mask respirator with a HEPA (high efficiency particulate air) filter is an acceptable alternative to masks and protective eye wear, but use of this equipment is not mandatory.

Accidental spills of potentially contaminated material should be decontaminated immediately by covering liberally with a disinfectant solution (5% hypochlorite or 10% formalin), **left to soak for 30 minutes**, and wiped up with absorbent material soaked in disinfectant. All biohazardous waste should be decontaminated by autoclaving. Contaminated equipment or instruments may be decontaminated with a hypochlorite solution, hydrogen peroxide, iodine, peracetic acid, 1% glutaraldehyde solution, formaldehyde, ethylene oxide, copper irradiation or other O.S.H.A. approved solutions, or by autoclaving or boiling for 10 minutes.

VII. Treatment

The key to successful treatment is prompt administration of an antimicrobial at the first suspicion of anthrax. During a biologic emergency, before susceptibility is determined (which may take several days), assume penicillin and tetracycline resistance and treat with ciprofloxacin at 400 mg IV every 12 hours. Penicillin is the antibiotic of choice for treating infections with penicillin-sensitive anthrax.

Treatment for Non-Pregnant Adults:

Inhalation anthrax (this regimen also recommended for gastrointestinal and meningeal anthrax)

- For **penicillin resistant anthrax,** administer *ciprofloxacin* at 400 mg IV every 8 to 12 hours (Alternative quinolone options include: ofloxacin 400 mg IV every 12 hours or levofloxacin 500 mg IV every 24 hours). If the isolate is tetracycline susceptible, *doxycycline* 200 mg initially, followed by 100mg IV every 12 hours is equally efficacious.

- For **penicillin susceptible anthrax,** administer *Penicillin G* IV 80,000 units/kg body weight in the first hour followed by a maintenance dose of 320,000 units/kg body weight/day. The average adult dose is 4 million units every 4 hours; can also be administered as 2 million units every 2 hours. (*Amoxicillin* 500 mg IV every 8 hours is an alternative regimen, with a dosing schedule that may be easier to administer in the event of a large-scale outbreak.)

- Supportive therapy is often required (e.g., volume expanders, vasopressor agents and oxygen). A tracheotomy may be needed if cervical edema compromises the airways.

Cutaneous anthrax

- *Mild disease*

  Penicillin susceptible anthrax - Potassium penicillin V orally at 30 mg/kg body weight/day in four equal portions every 6 hours, or amoxicillin 500 mg orally every 8 hours.

  Penicillin resistant anthrax - ciprofloxacin 500 mg orally every 12 hours or (if tetracycline susceptible) doxycycline 100 mg orally every 12 hours.

- *Extensive lesions*

  Penicillin susceptible anthrax - Penicillin G IV 2-4 million units every 4-6 hours or amoxicillin 500 mg IV every 8 hours.

  Penicillin resistant anthrax - Ciprofloxacin 400 mg IV every 12 hours or (if tetracycline susceptible) doxycycline 100 mg IV every 12 hours. When the edema and systemic symptoms have improved, treatment may be completed with the above oral regimens. In the absence of an aerosol exposure, therapy should be continued for 7-10 days. The skin lesions will continue to evolve despite the use of effective antibiotics but severe edema and systemic symptoms will be prevented. Glucosteroids for the first 3-4 days of treatment may reduce morbidity and mortality in severe cutaneous anthrax (malignant edema), particularly in the setting of laryngeal edema.

Alternative Therapies

******* In the event of severe penicillin allergy, documented resistance of *Bacillus anthracis* to penicillin, inability to administer the frequent IV dosing required for penicillin, or the exhaustion of penicillin supplies; **Ciprofloxacin (400 mg IV every 12 hours)**, **Ofloxacin (400 mg IV or orally every 8 to 12 hours)**, **Levofloxacin (500 mg IV or orally every 24 hours)** or **Doxycycline (100 mg IV every 12 hours)** (if proven susceptible) are the preferred alternatives.

In addition, the following drugs have been shown to have *in vitro* activity against anthrax and could potentially be used as alternative agents in the event of an emergency, if the preferred antimicrobials listed above are unavailable or in short supply:

erythromycin	aminoglycosides	vancomycin
imipenem	cephalothin/cefazolin	chloramphenicol
clindamycin	tetracycline	extended-spectrum penicillins

***** In vitro testing suggests that *B. anthracis* is generally resistant to sulfamethoxazole, trimethoprim, cefuroxime, cefotaxime, ceftriaxone, ceftazadime, and aztreonam. Therefore, these antibiotics should not be used for treatment or prophylaxis of anthrax infection.*****

Therapy in pediatric patients and pregnant women

- For **penicillin-resistant anthrax**, although ciprofloxacin is not generally given to children less than 16 years of age due to concerns about the development of arthropathy, the high mortality rate from anthrax infection weighs heavily in favor of using ciprofloxacin in this clinical situation. *Ciprofloxacin* should be given at 20-30 mg/kg/day orally or IV in 2 divided doses, not to exceed 1 gram/day.

- For **penicillin-susceptible anthrax**, *Penicillin G* is the drug of choice. The recommended intravenous dose **for children** with severe cutaneous anthrax, inhalation anthrax, or gastrointestinal anthrax is 250,000 units/kg body weight/day administered every 4 hours. *Amoxicillin* 500 mg IV every 8 hours for children > 20 kg and 40 mg/kg/day IV in divided doses every 8 hours for children < 20 kg, is an alternative antibiotic. Oral formulations can be used for milder disease or when IV therapy is not available.

- If ciprofloxacin supplies are exhausted and the patient is penicillin allergic or the anthrax strain is not susceptible to penicillin, *doxycycline* would be the preferred alternative agent (5 mg/kg/day IV or orally divided every 12 hours). Although doxycycline is not routinely administered to children < 8 years of age because of the risk of discoloration of teeth, the high mortality rate from systemic anthrax makes use of this agent the greater priority.

- *Penicillin G* is the drug of choice for **pregnant women,** if the isolate is penicillin-susceptible. The dosing schedule is as outlined for adults above. *Ciprofloxacin*, although not routinely prescribed during pregnancy, is the preferred alternative drug for penicillin-resistant strains, as tetracyclines can result in rare but serious liver toxicity during pregnancy. If doxycycline is used because of exhaustion of quinolone supplies or severe allergy to either penicillin or ciprofloxacin, liver function tests should be performed.

Vaccination and Duration of Therapy

- All patients treated for inhalational anthrax should also receive anthrax vaccine due to the risk that delayed germination of mediastinal spores can result in disease recurrence. **Three doses of vaccine (Days 0, 14 and 28) should be administered.**

- In the absence of available anthrax vaccine, antibiotic treatment for inhalation anthrax should be continued for 60 days. (Patients should be switched to oral medications, as soon as possible.) If anthrax vaccine is available for post-exposure vaccination, antibiotic therapy can be discontinued after three doses of vaccine (Days 0, 14, and 28) have been administered.

VIII. Isolation of Patients

Inhalation, cutaneous and gastrointestinal anthrax have never been transmitted directly from human-to-human. All staff should observe **Standard Precautions** when caring for patients with suspected or confirmed anthrax. In addition, the following is advised:

- For cutaneous anthrax, cover the lesion with a sterile dressing. Contact Wound and skin precautions should be observed for patients with skin lesions.

- Gloves should be worn for touching potentially infective material; gowns should be worn only if soiling is likely. Masks are not necessary, since patients with inhalation anthrax do not produce small particle aerosols containing sufficient spore counts (8,000 to 10,000 spores) to cause secondary infections.

- **HANDS MUST BE WASHED AFTER TOUCHING THE PATIENT OR POTENTIALLY CONTAMINATED ARTICLES AND BEFORE TAKING CARE OF ANOTHER PATIENT.**

- Patients do not require isolation rooms.

- Articles contaminated with infective material including bandages should be discarded and bagged and labeled before being sent for decontamination and reprocessing.

IX. Disposal of Infectious Waste

Use of tracking forms, containment, storage, packaging, treatment and disposal methods should be based upon the same rules as all other regulated medical wastes.

X. Autopsy and Handling of Corpses

All postmortem procedures should be performed using Universal Precautions.

- All persons performing or assisting in postmortem procedures must wear mandated P.P.E. (personal protective equipment) as delineated by O.S.H.A. guidelines.

- Instruments should be autoclaved or sterilized with a 10% bleach solution or other solutions approved by O.S.H.A. Surfaces contaminated during postmortem procedures should be decontaminated with an appropriate chemical germicide such as iodine, 10% hypochlorite or 5% phenol (carbolic acid).

XI. Management of Exposed Persons

In the event of a bioterrorist release of *Bacillus anthracis* spores, it may be difficult to define who has been exposed. Once the site of the attack is determined, all persons at the site of the release or downwind of the release (assuming an aerosol dispersal) would be considered potentially exposed.

Since inhalation anthrax does not spread from person to person, household and other contacts (such as healthcare workers caring for cases) of exposed persons are not

considered exposed and do not require prophylaxis (unless they too were exposed to the aerosolized anthrax spores at the time of the attack).

- **Inhalational exposures:** Initiation of antibiotic therapy quickly after exposure has been shown to markedly reduce the mortality of inhalation anthrax in animal studies. The best available prophylactic regimen is the combination of antibiotic therapy and vaccination. Antibiotic susceptibility information on clinical isolates should guide prophylactic antibiotic choices.
  While awaiting antibiotic susceptibility test results, or if susceptibility results confirm ***penicillin resistance***, begin therapy immediately with oral *ciprofloxacin* (500 mg po bid), *levofloxacin* (500 mg po per day), *ofloxacin* (400 mg po per bid), or *doxycycline* (100 mg po bid). If the isolate is ***penicillin susceptible***, *potassium penicillin V* (30 mg/kg/day in 4 divided doses) or *amoxicillin* (500 mg po every 8 hours) are the preferred preventive treatment.

- *Recommendations for prophylactic treatment of children, while awaiting antibiotic susceptibility results or if susceptibility results confirm* ***penicillin resistance****, include:* ciprofloxacin (20-30 mg per kg of body mass per day divided every 12 hours) or doxycycline (5 mg per kg of body mass per day divided every 12 hours). If the isolate is ***penicillin-susceptible***, all children should be treated with a penicillin antibiotic (for children weighing at least 20 kg, amoxicillin 500 mg po every 8 hours; for children < 20 kg, amoxicillin 40 mg per kg per day in divided doses every 8 hours).

- **Duration of antibiotic prophylaxis:** Therapy should be continued for at least 4 weeks, or until **three** doses of anthrax vaccine have been administered (Days 0, 14 and 28). **If vaccine is unavailable**, antibiotic prophylaxis should be continued for at least 60 days, and withdrawn under medical supervision.

- **Exposures through cuts, abrasions or injections:** Immediately wash the infected part, and apply a disinfectant solution such as hypochlorite solution. Promptly begin therapy as outlined under the treatment section for "Cutaneous anthrax-mild disease"; continue therapy for 7-10 days. Anthrax vaccine is not indicated.

- **Ingestional exposures:** Treat as for exposure by cuts or abrasions.

- **All persons exposed to anthrax should be instructed to watch for signs/symptoms of flu-like illness for at least 7 days.** Should such symptoms occur, patients must be immediately evaluated by a physician for the possible institution of intravenous antibiotic therapy.

- **VACCINATION** - An alum-absorbed, cell-free killed vaccine for anthrax has been developed and used primarily by the military and laboratory workers/veterinarians. The vaccine efficacy against cutaneous anthrax has been documented for humans; evidence for protection against inhalation and gastrointestinal anthrax is limited to animal studies.

  For prophylaxis, the vaccine is given parenterally (0.5mL subcutaneously) in three doses 2 weeks apart (Days 0, 14 and 28). Currently, there are limited vaccine supplies in the United States, and distribution is restricted to the military or persons at high-risk due to occupational exposures. (NOTE: Data from animal studies suggest that two doses of anthrax vaccine given two weeks apart may be sufficient, and in the setting of limited vaccine supplies may be a practical alternative).

  Adverse reactions to anthrax vaccine are not common. About 6% of patients may develop a local reaction and 2-3% experience mild systemic symptoms. **(NOTE: The FDA has only licensed the vaccine for use in healthy adults aged 18-65 years; the safety and efficacy of the vaccine for children and pregnant women has not been studied).**

  For current information about the availability of human anthrax vaccine, call the Placer County Health and Human Services, Communicable Disease Control at (530) 889-7141.

XII. Reporting to the Health Department

Human anthrax is a reportable disease in California. Although reporting of animal anthrax is not required by California regulations, we strongly urge reporting of

suspect animal cases as they may represent exposure to a bioterrorism attack. *All suspect human cases* should be reported immediately by phone:

- **During business hours**
  - Report suspect cases of *human and animal anthrax* to:
    Placer County Health and Human Services, Communicable Disease Control at **(530) 889-7141**

- **After business hours**
  - *Human and animal cases* call
    Placer County Health Officer Richard J. Burton, M.D., M.P.H., at **(530) 889-7119.**

XIII. References

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XIV. **Table 1: Inhalational Anthrax Treatment and Prophylaxis**

	Therapy	**Prophylaxis***
	Adult Doses	**Adult Doses**
Susceptibility Results Unknown or Penicillin- Resistant**	Ciprofloxacin 400mg IV q 8- 12h (*Alternative quinolones include:* ofloxacin 400mg IV q 8-12h or levofloxacin (500mg IV q 24h) Doxycycline 200mg IV x 1, then 100mg IV q 12h (*if tetracycline-susceptible*)	Ciprofloxacin 500mg po bid (*Alternative quinolones include:* ofloxacin 400mg po q 8- 12h or levofloxacin (500mg po q 24h Doxycycline 100mg po bid (*if tetracycline susceptible*)
Penicillin Susceptible	Penicillin G 80,000 units per kg in 1st hour followed by 320,000 units/kg/day. (*Average adult dose is 4 million units q 4hr or 2 million units q 2h*) Amoxicillin 500mg IV q 8h	Penicillin VK 30mg/kg/d in 4 divided doses Amoxicillin 500mg po q 8h

	Pediatric Doses	Pediatric Doses
Susceptibility results unknown or penicillin-resistant	Ciprofloxacin 20-30mg/kg/day IV in 2 divided doses (*maximum daily dose not to exceed 1 gram/d*) Doxycycline (*if ciprofloxacin not available*) 4 mg/kg/d IV in 2 divided doses	Ciprofloxacin 20-30mg/kg per day po divided in 2 doses Doxycycline 5mg/kg/per day in 2 divided doses
Penicillin-susceptibility	Penicillin G 250,000 units/kg per day IV administered every 4 hours Amoxacillin 500mg IV q 8h if > 20kg or 40mg/kg per day IV divided into 3 doses if < 20kg	Penicillin VK 30 mg/kg per day po administered in 4 divided doses Amoxicillin 500mg po q 8h if > 20kg or 40mg/kg per day po divided in 3 doses if < 20kg

* Antibiotic prophylaxis should be continued for 60 days if anthrax vaccine is not available (*or if vaccine is available, antibiotics should be continued until 3rd dose of vaccine has been administered*).

** In pregnant women, penicillin-resistant anthrax should be treated with ciprofloxacin. If doxycycline is used, liver function tests should be monitored closely.

NOctober 2001

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PLAGUE

ALL SUSPECT CASES OF PLAGUE MUST BE REPORTED IMMEDIATELY TO THE HEALTH AND HUMAN SERVICES COMMUNICABLE DISEASE CONTROL:

During business hours: (530) 889-7141
After hours (Health Officer Richard J. Burton, M.D., M.P.H.): (530) 889-7119

(In the event that you are unable to reach a Communicable Disease Control Contact, please call the Placer County Office of Emergency Services at (530) 886-5300 during business hours, or 24-hour dispatch at (530) 886-5375 after business hours.)

Epidemiology**:**

- Highly infectious after aerosolization
- Person-to-person and animal-to-human transmission can occur with pneumonic plague via respiratory droplet

Clinical:

- Incubation period is 1-3 days (ranges up to 7 days)
- Aerosolization would most likely result in pneumonic plague
- Pneumonic plague presents with acute onset of high fevers, chills, headache, malaise and a productive cough, that is initially watery before becoming bloody

Laboratory Diagnosis:

- Bacterial cultures (blood, sputum, or lymph node aspirate specimens) should be handled in a Biosafety Level 2 facility
- Wright, Giemsa, or Wayson stain shows gram negative coccobacilli with bipolar "safety-pin" appearance
- Organism grows slowly (48 hrs for observable growth) on standard blood and MacConkey agar
- Immunoflourescent staining for capsule (F1 antigen) is diagnostic
- Fluorescent antibody tests available through The Laboratory Response Network
- Contact the Placer County Public Health Laboratory for assistance

Patient Isolation:

- Strict respiratory isolation with droplet precautions (gown, gloves, and eye protection) until the patient has received at least 48 hours of antibiotic therapy and shows clinical improvement

Treatment:

- Streptomycin (1 g IM bid) or gentamicin (5 mg/kg IM or IV qd) are the preferred antibiotics
- Tetracyclines or flouroquinolones are alternative choices
- Co-trimoxazole is recommended for pregnant women and children between the ages of 2 months and 8 years
- Chloramphenicol should be used for plague meningitis

Prophylaxis:

- Antibiotic prophylaxis is recommended for all persons exposed to the aerosol or persons in close physical contact with a confirmed case
- Tetracyclines or flouroquinolones are recommended for 7 days from last exposure to a case

Plague as a Biological Weapon
Medical and Public Health Management

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for the Working Group on Civilian Biodefense

Objective The Working Group on Civilian Biodefense has developed consensus-based recommendations for measures to be taken by medical and public health professionals following the use of plague as a biological weapon against a civilian population.

Participants The working group included 25 representatives from major academic medical centers and research, government, military, public health, and emergency management institutions and agencies.

Evidence MEDLINE databases were searched from January 1966 to June 1998 for the Medical Subject Headings *plague*, *Yersinia pestis*, *biological weapon*, *biological terrorism*, *biological warfare*, and *biowarfare*. Review of the bibliographies of the references identified by this search led to subsequent identification of relevant references published prior to 1966. In addition, participants identified other unpublished references and sources. Additional MEDLINE searches were conducted through January 2000.

Consensus Process The first draft of the consensus statement was a synthesis of information obtained in the formal evidence-gathering process. The working group was convened to review drafts of the document in October 1998 and May 1999. The final statement incorporates all relevant evidence obtained by the literature search in conjunction with final consensus recommendations supported by all working group members.

Conclusions An aerosolized plague weapon could cause fever, cough, chest pain, and hemoptysis with signs consistent with severe pneumonia 1 to 6 days after exposure. Rapid evolution of disease would occur in the 2 to 4 days after symptom onset and would lead to septic shock with high mortality without early treatment. Early treatment and prophylaxis with streptomycin or gentamicin or the tetracycline or fluoroquinolone classes of antimicrobials would be advised.

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THIS IS THE THIRD ARTICLE IN A series entitled *Medical and Public Health Management Following the Use of a Biological Weapon: Consensus Statements of the Working Group on Civilian Biodefense*.[1,2] The working group has identified a limited number of agents that, if used as weapons, could cause disease and death in sufficient numbers to cripple a city or region. These agents also comprise the top of the list of "Critical Biological Agents" recently developed by the Centers for Disease Control and Prevention (CDC).[3] *Yersinia pestis*, the causative agent of plague, is one of the most serious of these. Given the availability of *Y pestis* around the world, capacity for its mass production and aerosol dissemination, difficulty in preventing such activities, high fatality rate of pneumonic plague, and potential for secondary spread of cases during an epidemic, the potential use of plague as a biological weapon is of great concern.

CONSENSUS METHODS

The working group comprised 25 representatives from major academic medical centers and research, government, military, public health, and emergency management institutions and agencies.

MEDLINE databases were searched from January 1966 to June 1998 using the Medical Subject Headings (MeSH) *plague*, *Yersinia pestis*, *biological weapon*, *biological terrorism*, *biological warfare*, and *biowarfare*. Review of the bibliographies of the references identified by

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this search led to subsequent identification of relevant references published prior to 1966. In addition, participants identified other unpublished references and sources in their fields of expertise. Additional MEDLINE searches were conducted through January 2000 during the review and revisions of the statement.

The first draft of the consensus statement was a synthesis of information obtained in the initial formal evidence-gathering process. Members of the working group were asked to make formal written comments on this first draft of the document in September 1998. The document was revised incorporating changes suggested by members of the working group, which was convened to review the second draft of the document on October 30, 1998. Following this meeting and a second meeting of the working group on May 24, 1999, a third draft of the document was completed, reviewed, and revised. Working group members had a final opportunity to review the document and suggest revisions. The final document incorporates all relevant evidence obtained by the literature search in conjunction with consensus recommendations supported by all working group members.

The assessment and recommendations provided herein represent the best professional judgment of the working group based on data and expertise currently available. The conclusions and recommendations need to be regularly reassessed as new information becomes available.

HISTORY AND POTENTIAL AS A BIOTERRORIST AGENT

In AD 541, the first recorded plague pandemic began in Egypt and swept across Europe with attributable population losses of between 50% and 60% in North Africa, Europe, and central and southern Asia.[4] The second plague pandemic, also known as the *black death* or *great pestilence*, began in 1346 and eventually killed 20 to 30 million people in Europe, one third of the European population.[5] Plague spread slowly and inexorably from village to village by infected rats and humans or more quickly from country to country by ships. The pandemic lasted more than 130 years and had major political, cultural, and religious ramifications. The third pandemic began in China in 1855, spread to all inhabited continents, and ultimately killed more than 12 million people in India and China alone.[4] Small outbreaks of plague continue to occur throughout the world.[4,5]

Advances in living conditions, public health, and antibiotic therapy make future pandemics improbable. However, plague outbreaks following use of a biological weapon are a plausible threat. In World War II, a secret branch of the Japanese army, Unit 731, is reported to have dropped plague-infected fleas over populated areas of China, thereby causing outbreaks of plague.[6] In the ensuing years, the biological weapons programs of the United States and the Soviet Union developed techniques to aerosolize plague directly, eliminating dependence on the unpredictable flea vector. In 1970, the World Health Organization (WHO) reported that, in a worst-case scenario, if 50 kg of *Y pestis* were released as an aerosol over a city of 5 million, pneumonic plague could occur in as many as 150 000 persons, 36 000 of whom would be expected to die.[7] The plague bacilli would remain viable as an aerosol for 1 hour for a distance of up to 10 km. Significant numbers of city inhabitants might attempt to flee, further spreading the disease.[7]

While US scientists had not succeeded in making quantities of plague organisms sufficient to use as an effective weapon by the time the US offensive program was terminated in 1970, Soviet scientists were able to manufacture large quantities of the agent suitable for placing into weapons.[8] More than 10 institutes and thousands of scientists were reported to have worked with plague in the former Soviet Union.[8] In contrast, few scientists in the United States study this disease.[9]

There is little published information indicating actions of autonomous groups or individuals seeking to develop plague as a weapon. However, in 1995 in Ohio, a microbiologist with suspect motives was arrested after fraudulently acquiring *Y pestis* by mail.[10] New antiterrorism legislation was introduced in reaction.

EPIDEMIOLOGY

Naturally Occurring Plague

Human plague most commonly occurs when plague-infected fleas bite humans who then develop bubonic plague. As a prelude to human epidemics, rats frequently die in large numbers, precipitating the movement of the flea population from its natural rat reservoir to humans. Although most persons infected by this route develop bubonic plague, a small minority will develop sepsis with no bubo, a form of plague termed *primary septicemic plague*. Neither bubonic nor septicemic plague spreads directly from person to person. A small percentage of patients with bubonic or septicemic plague develop secondary pneumonic plague and can then spread the disease by respiratory droplet. Persons contracting the disease by this route develop primary pneumonic plague.[11]

Plague remains an enzootic infection of rats, ground squirrels, prairie dogs, and other rodents on every populated continent except Australia.[4] Worldwide, on average in the last 50 years, 1700 cases have been reported annually.[4] In the United States, 390 cases of plague were reported from 1947 to 1996, 84% of which were bubonic, 13% septicemic, and 2% pneumonic. Concomitant case fatality rates were 14%, 22%, and 57%, respectively.[12] Most US cases were in New Mexico, Arizona, Colorado, and California. Of the 15 cases following exposure to domestic cats with plague, 4 were primary pneumonic plague.[13] In the United States, the last case of human-to-human transmission of plague occurred in Los Angeles in 1924.[14,15]

Although pneumonic plague has rarely been the dominant manifestation of the disease, large outbreaks of pneumonic plague have occurred.[16] In an outbreak in Manchuria in 1910-1911, as many as 60 000 persons developed pneumonic plague; a second large Manchurian pneumonic plague outbreak occurred in 1920-1921.[16,17] As

would be anticipated in the preantibiotic era, nearly 100% of these cases were reported to be fatal.[16,17] Reports from the Manchurian outbreaks suggested that indoor contacts of affected patients were at higher risk than outdoor contacts and that cold temperature, increased humidity, and crowding contributed to increased spread.[14,15] In northern India, there was an epidemic of pneumonic plague with 1400 deaths reported at about the same time.[15] While epidemics of pneumonic plague of this scale have not occurred since, smaller epidemics of pneumonic plague have occurred recently. In 1997 in Madagascar, 1 patient with bubonic plague and secondary pneumonic infection transmitted pneumonic plague to 18 persons, 8 of whom died.[18]

Plague Following Use of a Biological Weapon

The epidemiology of plague following its use as a biological weapon would differ substantially from that of naturally occurring infection. Intentional dissemination of plague would most probably occur via an aerosol of *Y pestis*, a mechanism that has been shown to produce disease in nonhuman primates.[19] A pneumonic plague outbreak would result with symptoms initially resembling those of other severe respiratory illnesses. The size of the outbreak would depend on factors including the quantity of biological agent used, characteristics of the strain, environmental conditions, and methods of aerosolization. Symptoms would begin to occur 1 to 6 days following exposure, and people would die quickly following onset of symptoms.[16] Indications that plague had been artificially disseminated would be the occurrence of cases in locations not known to have enzootic infection, in persons without known risk factors, and in the absence of prior rodent deaths.

MICROBIOLOGY AND VIRULENCE FACTORS

Y pestis is a nonmotile, gram-negative bacillus, sometimes coccobacillus, that shows bipolar (also termed *safety pin*) staining with Wright, Giemsa, or Wayson stain (FIGURE 1).[20] *Y pestis* is a lactose nonfermenter, urease and indole negative, and a member of the Enterobacteriaceae family.[21] It grows optimally at 28°C on blood agar or MacConkey agar, typically requiring 48 hours for observable growth, but colonies are initially much smaller than other Enterobacteriaceae and may be overlooked. *Y pestis* has a number of virulence factors that enable it to survive in humans by facilitating use of host nutrients, causing damage to host cells, and subverting phagocytosis and other host defense mechanisms.[4,11,21,22]

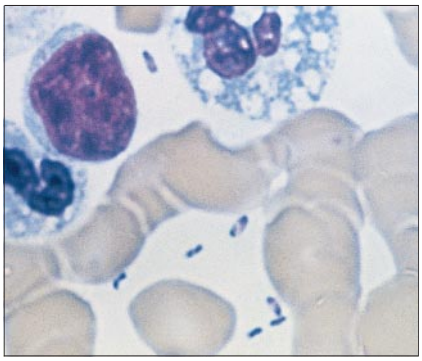
PATHOGENESIS AND CLINICAL MANIFESTATIONS

Naturally Occurring Plague

In most cases of naturally occurring plague, the bite by a plague-infected flea leads to the inoculation of up to thousands of organisms into a patient's skin. The bacteria migrate through cutaneous lymphatics to regional lymph nodes where they are phagocytosed but resist destruction. They rapidly multiply, causing destruction and necrosis of lymph node architecture with subsequent bacteremia, septicemia, and endotoxemia that can lead quickly to shock, disseminated intravascular coagulation, and coma.[21]

Patients typically develop symptoms of bubonic plague 2 to 8 days after being bitten by an infected flea. There is sudden onset of fever, chills, and weakness and the development of an acutely swollen tender lymph node, or bubo, up to 1 day later.[23] The bubo most typically develops in the groin, axilla, or cervical region (FIGURE 2, A) and is often so painful that it prevents patients from moving the affected area of the body. Buboes are 1 to 10 cm in diameter, and the overlying skin is erythematous.[21] They are extremely tender, nonfluctuant, and warm and are often associated with considerable surrounding edema, but seldom lymphangitis. Rarely, buboes become fluctuant and suppurate. In addition, pustules or skin ulcerations may occur at the site of the flea bite in a minority of patients. A small minority of patients infected by fleas develop *Y pestis* septicemia without a discernable bubo, the form of disease termed *primary septicemic plague*.[23] Septicemia can also arise secondary to bubonic plague.[21] Septicemic plague may lead to disseminated intravascular coagulation, necrosis of small vessels, and purpuric skin lesions (Figure 2, B). Gangrene of acral regions such as the digits and nose may also occur in advanced disease, a process believed responsible for the name *black death* in the second plague pandemic (Figure 2, C).[21] However, the finding of gangrene would not be expected to be helpful in diagnosing the disease in the early stages of illness when early antibiotic treatment could be lifesaving.

Figure 1. Peripheral Blood Smear From Patient With Septicemic Plague

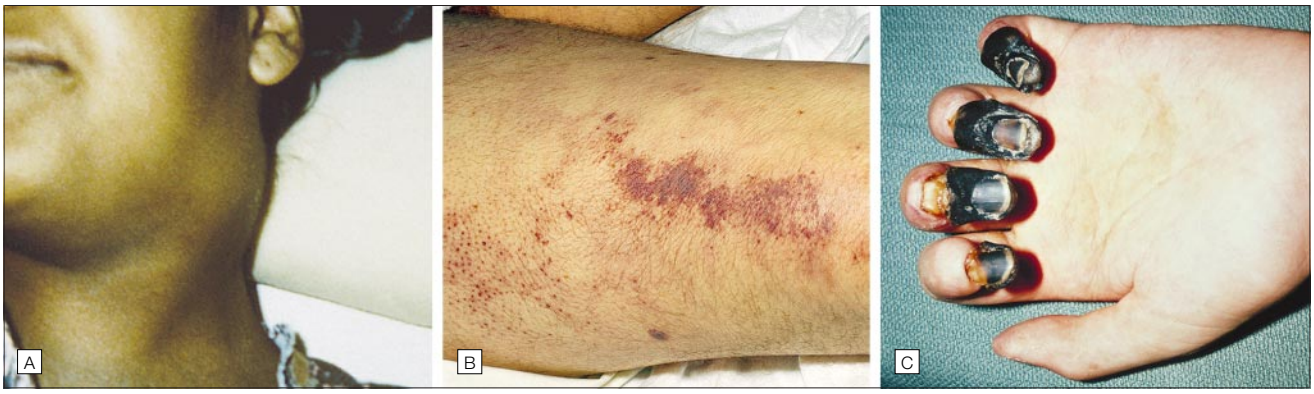


Smear shows characteristic bipolar staining of *Yersinia pestis* bacilli (Wright-Giemsa stain; magnification, ×1000). Figure from Centers for Disease Control and Prevention, Division of Vector-Borne Infectious Diseases, Fort Collins, Colo.

Secondary pneumonic plague develops in a minority of patients with bubonic or primary septicemic plague—approximately 12% of total cases in the United States over the last 50 years.[4] This process, termed *secondary pneumonic plague*, develops via hematogenous spread of plague bacilli to the lungs. Patients commonly have symptoms of severe bronchopneumonia, chest pain, dyspnea, cough, and hemoptysis.[16,21]

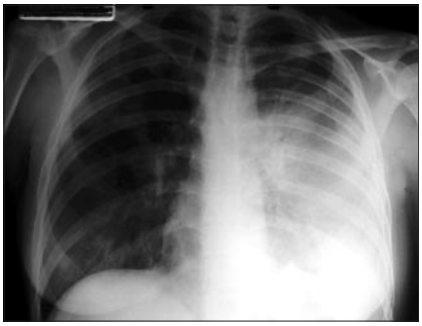
Primary pneumonic plague resulting from the inhalation of plague bacilli occurs rarely in the United States.[12] Reports of 2 recent cases of primary pneumonic plague, contracted after handling cats with pneumonic plague, reveal that both patients had pneumonic symptoms as well as prominent gastro-

Figure 2. Patients With Naturally Occurring Plague



A, Cervical bubo in patient with bubonic plague; B, petechial and ecchymotic bleeding into the skin in patient with septicemic plague; and C, gangrene of the digits during the recovery phase of illness of patient shown in B. In plague following the use of a biological weapon, presence of cervical bubo is rare; purpuric skin lesions and necrotic digits occur only in advanced disease and would not be helpful in diagnosing the disease in the early stages of illness when antibiotic treatment can be lifesaving. Figures from Centers for Disease Control and Prevention, Division of Vector-Borne Infectious Diseases, Fort Collins, Colo.

Figure 3. Chest Radiograph of Patient With Primary Pneumonic Plague



Radiograph shows extensive lobar consolidation in left lower and left middle lung fields. Figure from Centers for Disease Control and Prevention, Division of Vector-Borne Infectious Diseases, Fort Collins, Colo.

intestinal symptoms including nausea, vomiting, abdominal pain, and diarrhea. Diagnosis and treatment were delayed more than 24 hours after symptom onset in both patients, both of whom died.[24,25]

Less common plague syndromes include plague meningitis and plague pharyngitis. Plague meningitis follows the hematogenous seeding of bacilli into the meninges and is associated with fever and meningismus. Plague pharyngitis follows inhalation or ingestion of plague bacilli and is associated with cervical lymphadenopathy.[21]

Plague Following Use of a Biological Weapon

The pathogenesis and clinical manifestations of plague following a biological attack would be notably different than naturally occurring plague. Inhaled aerosolized *Y pestis* bacilli would cause primary pneumonic plague. The time from exposure to aerosolized plague bacilli until development of first symptoms in humans and nonhuman primates has been found to be 1 to 6 days and most often, 2 to 4 days.[12,16,19,26] The first sign of illness would be expected to be fever with cough and dyspnea, sometimes with the production of bloody, watery, or less commonly, purulent sputum.[16,19,27] Prominent gastrointestinal symptoms, including nausea, vomiting, abdominal pain, and diarrhea, might be present.[24,25]

The ensuing clinical findings of primary pneumonic plague are similar to those of any severe rapidly progressive pneumonia and are quite similar to those of secondary pneumonic plague. Clinicopathological features may help distinguish primary from secondary pneumonic plague.[11] In contrast to secondary pneumonic plague, features of primary pneumonic plague would include absence of buboes (except, rarely, cervical buboes) and, on pathologic examination, pulmonary disease with areas of profound lobular exudation and bacillary aggregation.[11] Chest radiographic findings are variable but bilateral infiltrates or consolidation are common (FIGURE 3).[22]

Laboratory studies may reveal leukocytosis with toxic granulations, coagulation abnormalities, aminotransferase elevations, azotemia, and other evidence of multiorgan failure. All are nonspecific findings associated with sepsis and systemic inflammatory response syndrome.[11,21]

The time from respiratory exposure to death in humans is reported to have been between 2 to 6 days in epidemics during the preantibiotic era, with a mean of 2 to 4 days in most epidemics.[16]

DIAGNOSIS

Given the rarity of plague infection and the possibility that early cases are a harbinger of a larger epidemic, the first clinical or laboratory suspicion of plague must lead to immediate notification of the hospital epidemiologist or infection control practitioner, health department, and the local or state health laboratory. Definitive tests can thereby be arranged rapidly through a state reference laboratory or, as necessary, the Diagnostic and Reference Laboratory of the CDC and early interventions instituted.

The early diagnosis of plague requires a high index of suspicion in naturally occurring cases and even more so following the use of a biological weapon. There are no effective environmental warning systems to detect an aerosol of plague bacilli.[28]

The first indication of a clandestine terrorist attack with plague would most likely be a sudden outbreak of illness presenting as severe pneumonia and

sepsis. If there are only small numbers of cases, the possibility of them being plague may be at first overlooked given the clinical similarity to other bacterial or viral pneumonias and that few Western physicians have ever seen a case of pneumonic plague. However, the sudden appearance of a large number of previously healthy patients with fever, cough, shortness of breath, chest pain, and a fulminant course leading to death should immediately suggest the possibility of pneumonic plague or inhalational anthrax.[1] The presence of hemoptysis in this setting would strongly suggest plague (TABLE 1).[22]

Table 1. Diagnosis of Pneumonic Plague Infection Following Use of a Biological Weapon

Epidemiology and symptoms	Sudden appearance of many persons with fever, cough, shortness of breath, hemoptysis, and chest pain
	Gastrointestinal symptoms common (eg, nausea, vomiting, abdominal pain, and diarrhea)
	Patients have fulminant course and high mortality
Clinical signs	Tachypnea, dyspnea, and cyanosis
	Pneumonic consolidation on chest examination
	Sepsis, shock, and organ failure
	Infrequent presence of cervical bubo
	(Purpuric skin lesions and necrotic digits only in advanced disease)
Laboratory studies	Sputum, blood, or lymph node aspirate
	Gram-negative bacilli with bipolar (safety pin) staining on Wright, Giemsa, or Wayson stain
	Rapid diagnostic tests available only at some health departments, the Centers for Disease Control and Prevention, and military laboratories
	Pulmonary infiltrates or consolidation on chest radiograph
Pathology	Lobular exudation, bacillary aggregation, and areas of necrosis in pulmonary parenchyma

There are no widely available rapid diagnostic tests for plague.[28] Tests that would be used to confirm a suspected diagnosis—antigen detection, IgM enzyme immunoassay, immunostaining, and polymerase chain reaction—are available only at some state health departments, the CDC, and military laboratories.[21] The routinely used passive hemagglutination antibody detection assay is typically only of retrospective value since several days to weeks usually pass after disease onset before antibodies develop.

Microbiologic studies are important in the diagnosis of pneumonic plague. A Gram stain of sputum or blood may reveal gram-negative bacilli or coccobacilli.[4,21,29] A Wright, Giemsa, or Wayson stain will often show bipolar staining (Figure 1), and direct fluorescent antibody testing, if available, may be positive. In the unlikely event that a cervical bubo is present in pneumonic plague, an aspirate (obtained with a 20-gauge needle and a 10-mL syringe containing 1-2 mL of sterile saline for infusing the node) may be cultured and similarly stained (Table 1).[22]

Cultures of sputum, blood, or lymph node aspirate should demonstrate growth approximately 24 to 48 hours after inoculation. Most microbiology laboratories use either automated or semiautomated bacterial identification systems. Some of these systems may misidentify *Y pestis*.[12,30] In laboratories without automated bacterial identification, as many as 6 days may be required for identification, and there is some chance that the diagnosis may be missed entirely. Approaches for biochemical characterization of *Y pestis* are described in detail elsewhere.[20]

If a laboratory using automated or nonautomated techniques is notified that plague is suspected, it should split the culture: 1 culture incubated at 28°C for rapid growth and the second culture incubated at 37°C for identification of the diagnostic capsular (F_1) antigen. Using these methods, up to 72 hours may be required following specimen procurement to make the identification (May Chu, PhD, CDC, Fort Collins, Colo, written communication, April 9, 1999). Antibiotic susceptibility testing should be performed at a reference laboratory because of the lack of standardized susceptibility testing procedures for *Y pestis*. A process establishing criteria and training measures for laboratory diagnosis of this disease is being undertaken jointly by the Association of Public Health Laboratories and the CDC.

VACCINATION

The US-licensed formaldehyde-killed whole bacilli vaccine was discontinued by its manufacturers in 1999 and is no longer available. Plans for future licensure and production are unclear. This killed vaccine demonstrated efficacy in preventing or ameliorating bubonic disease, but it does not prevent or ameliorate the development of primary pneumonic plague.[19,31] It was used in special circumstances for individuals deemed to be at high risk of developing plague, such as military personnel working in plague endemic areas, microbiologists working with *Y pestis* in the laboratory, or researchers working with plague-infected rats or fleas. Research is ongoing in the pursuit of a vaccine that protects against primary pneumonic plague.[22,32]

THERAPY

Recommendations for the use of antibiotics following a plague biological weapon exposure are conditioned by the lack of published trials in treating plague in humans, limited number of studies in animals, and possible requirement to treat large numbers of persons. A number of possible therapeutic regimens for treating plague have yet to be adequately studied or submitted for approval to the Food and Drug Administration (FDA). For these reasons, the working group offers consensus recommendations based on the best available evidence. The recommendations do not necessarily represent uses currently approved by the FDA or an official position on the part of any of the federal agencies whose scientists participated in these discussions. Recommendations will need to be revised as further relevant information becomes available.

In the United States during the last 50 years, 4 of the 7 reported primary pneumonic plague patients died.[12] Fatality rates depend on various factors including time to initiation of antibiotics, access to advanced supportive care, and the dose of inhaled bacilli. The fatality rate of patients with pneumonic plague when treatment is delayed more than 24 hours after symptom onset is extremely high.[14,24,25,33]

Historically, the preferred treatment for plague infection has been streptomycin, an FDA-approved treatment for plague.[21,34,35] Administered early during the disease, streptomycin has reduced overall plague mortality to the 5% to 14% range.[12,21,34] However, streptomycin is infrequently used in the United States and only modest supplies are available.[35] Gentamicin is not FDA approved for the treatment of plague but has been used successfully[36-39] and is recommended as an acceptable alternative by experts.[23,40] In 1 case series, 8 patients with plague were treated with gentamicin with morbidity or mortality equivalent to that of patients treated with streptomycin (Lucy Boulanger, MD, Indian Health Services, Crown Point, NM, written communication, July 20, 1999). In vitro studies and an in vivo study in mice show equal or improved activity of gentamicin against many strains of *Y pestis* when compared with streptomycin.[41,42] In addition, gentamicin is widely available, inexpensive, and can be given once daily.[35]

Tetracycline and doxycycline also have been used in the treatment and prophylaxis of plague; both are FDA approved for these purposes. In vitro studies have shown that *Y pestis* susceptibility to tetracycline[43] and doxycycline[41,44] is equivalent to that of the aminoglycosides. In another investigation, 13% of *Y pestis* strains in Madagascar were found to have some in vitro resistance to tetracycline.[45] Experimental murine models of *Y pestis* infection have yielded data that are difficult to extrapolate to humans. Some mouse studies have shown doxycycline to be a highly efficacious treatment of infection[44,46] or prophylaxis[47] against naturally occurring plague strains. Experimental murine infection with F_1-deficient variants of *Y pestis* have shown decreased efficacy of doxycycline,[47,48] but only 1 human case of F_1-deficient plague infection has been reported.[49] Russell and colleagues[50] reported poor efficacy of doxycycline against plague-infected mice, but the dosing schedules used in this experiment would have failed to maintain drug levels above the minimum inhibitory concentration due to the short half-life of doxycycline in mice. In another study, doxycycline failed to prevent death in mice intraperitoneally infected with 29 to 290 000 times the median lethal inocula of *Y pestis*.[51]

There are no controlled clinical trials comparing either tetracycline or doxycycline to aminoglycoside in the treatment of plague, but anecdotal case series and a number of medical authorities support use of this class of antimicrobials for prophylaxis and for therapy in the event that streptomycin or gentamicin cannot be administered.[23,27,38-40,52-54] Based on evidence from in vitro studies, animal studies, and uncontrolled human data, the working group recommends that the tetracycline class of antibiotics be used to treat pneumonic plague if aminoglycoside therapy cannot be administered. This might be the case in a mass casualty scenario when parenteral therapy was either unavailable or impractical. Doxycycline would be considered pharmacologically superior to other antibiotics in the tetracycline class for this indication, because it is well absorbed without food interactions, is well distributed with good tissue penetration, and has a long half-life.[35]

The fluoroquinolone family of antimicrobials has demonstrated efficacy in animal studies. Ciprofloxacin has been demonstrated to be at least as efficacious as aminoglycosides and tetracyclines in studies of mice with experimentally induced pneumonic plague.[44,50,51] In vitro studies also suggest equivalent or greater activity of ciprofloxacin, levofloxacin, and ofloxacin against *Y pestis* when compared with aminoglycosides or tetracyclines.[41,55] However, there have been no trials of fluoroquinolones in human plague, and they are not FDA approved for this indication.

Chloramphenicol has been used to treat plague infection and has been recommended for treatment of plague meningitis because of its ability to cross the blood-brain barrier.[21,34] However, human clinical trials demonstrating the superiority of chloramphenicol in the therapy of classic plague infection or plague meningitis have not been performed. It has been associated with dose dependent hematologic abnormalities and with rare idiosyncratic fatal aplastic anemia.[35]

A number of different sulfonamides have been used successfully in the treatment of human plague infection: sulfathiazole,[56] sulfadiazine, sulfamerazine, and trimethoprim-sulfamethoxazole.[57,58] The 1970 WHO analysis reported that sulfadiazine reduced mortality for bubonic plague but was ineffective against pneumonic plague and was less effective than tetracycline overall.[59] In a study comparing trimethoprim-sulfamethoxazole with streptomycin, patients treated with trimethoprim-sulfamethoxazole had a longer median duration of fever and a higher incidence of complications.[58] Authorities have generally considered trimethoprim-sulfamethoxazole a second-tier choice.[21,23,34] Some have recommended sulfonamides only in the setting of pediatric prophylaxis.[22] No sulfonamides have been FDA approved for the treatment of plague.

Antimicrobials that have been shown to have poor or only modest efficacy in animal studies have included rifampin, aztreonam, ceftazidime, cefotetan, and cefazolin; these antibiotics should not be used.[42]

Antibiotic resistance patterns must also be considered in making treatment recommendations. Naturally occurring antibiotic resistance to the tetracycline class of drugs has occurred rarely.[4] Recently, a plasmid-mediated multidrug-resistant strain was isolated in Madagascar.[60] A report published by Russian scientists cited quinolone-resistant *Y pestis*.[61] There have been assertions that Russian scientists have en-

gineered multidrug-resistant strains of *Y pestis*,[8] although there is as yet no scientific publication confirming this.

Recommendations for Antibiotic Therapy

The working group treatment recommendations are based on literature reports on treatment of human disease, reports of studies in animal models, reports on in vitro susceptibility testing, and antibiotic safety. Should antibiotic susceptibility testing reveal resistance, proper antibiotic substitution would need to be made.

In a contained casualty setting, a situation in which a modest number of patients require treatment, the working group recommends parenteral antibiotic therapy (TABLE 2). Preferred parenteral forms of the antimicrobials streptomycin or gentamicin are recommended. However, in a mass casualty setting, intravenous or intramuscular therapy may not be possible for reasons of patient care logistics and/or exhaustion of equipment and antibiotic supplies, and parenteral therapy will need to be supplanted by oral therapy. In a mass casualty setting, the working group recommends oral therapy, preferably with doxycycline (or tetracycline) or ciprofloxacin (Table 2).

Patients with pneumonic plague will require substantial advanced medical supportive care in addition to antimicrobial therapy. Complications of gram-negative sepsis would be expected, including adult respiratory distress syndrome, disseminated intravascular coagulation, shock, and multiorgan failure.[23]

Once it was known or strongly suspected that pneumonic plague cases were occurring, anyone with fever or cough in the presumed area of exposure should be immediately treated with antimicrobials for presumptive pneumonic plague. Delaying therapy until confirmatory testing is performed would greatly decrease survival.[59] Clinical deterioration of patients despite early initiation of empiric therapy could signal antimicrobial resistance and should be promptly evaluated.

Table 2. Working Group Recommendations for Treatment of Patients With Pneumonic Plague in the Contained and Mass Casualty Settings and for Postexposure Prophylaxis*

Patient Category	Recommended Therapy
	Contained Casualty Setting
Adults	Preferred choices Streptomycin, 1 g IM twice daily
	Gentamicin, 5 mg/kg IM or IV once daily or 2 mg/kg loading dose followed by 1.7 mg/kg IM or IV 3 times daily†
	Alternative choices Doxycycline, 100 mg IV twice daily or 200 mg IV once daily
	Ciprofloxacin, 400 mg IV twice daily‡
	Chloramphenicol, 25 mg/kg IV 4 times daily§
Children‖	Preferred choices Streptomycin, 15 mg/kg IM twice daily (maximum daily dose, 2 g)
	Gentamicin, 2.5 mg/kg IM or IV 3 times daily†
	Alternative choices Doxycycline, If ≥45 kg, give adult dosage
	If <45 kg, give 2.2 mg/kg IV twice daily (maximum, 200 mg/d)
	Ciprofloxacin, 15 mg/kg IV twice daily‡
	Chloramphenicol, 25 mg/kg IV 4 times daily§
Pregnant women¶	Preferred choice Gentamicin, 5 mg/kg IM or IV once daily or 2 mg/kg loading dose followed by 1.7 mg/kg IM or IV 3 times daily†
	Alternative choices Doxycycline, 100 mg IV twice daily or 200 mg IV once daily
	Ciprofloxacin, 400 mg IV twice daily‡
	Mass Casualty Setting and Postexposure Prophylaxis#
Adults	Preferred choices Doxycycline, 100 mg orally twice daily††
	Ciprofloxacin, 500 mg orally twice daily‡
	Alternative choice Chloramphenicol, 25 mg/kg orally 4 times daily§**
Children‖	Preferred choice Doxycycline,†† If ≥45 kg, give adult dosage
	If <45 kg, then give 2.2 mg/kg orally twice daily
	Ciprofloxacin, 20 mg/kg orally twice daily
	Alternative choices Chloramphenicol, 25 mg/kg orally 4 times daily§**
Pregnant women¶	Preferred choices Doxycycline, 100 mg orally twice daily††
	Ciprofloxacin, 500 mg orally twice daily
	Alternative choices Chloramphenicol, 25 mg/kg orally 4 times daily§**

*These are consensus recommendations of the Working Group on Civilian Biodefense and are not necessarily approved by the Food and Drug Administration. See "Therapy" section for explanations. One antimicrobial agent should be selected. Therapy should be continued for 10 days. Oral therapy should be substituted when patient's condition improves. IM indicates intramuscularly; IV, intravenously.

†Aminoglycosides must be adjusted according to renal function. Evidence suggests that gentamicin, 5 mg/kg IM or IV once daily, would be efficacious in children, although this is not yet widely accepted in clinical practice. Neonates up to 1 week of age and premature infants should receive gentamicin, 2.5 mg/kg IV twice daily.

‡Other fluoroquinolones can be substituted at doses appropriate for age. Ciprofloxacin dosage should not exceed 1 g/d in children.

§Concentration should be maintained between 5 and 20 µg/mL. Concentrations greater than 25 µg/mL can cause reversible bone marrow suppression.[35,62]

‖Refer to "Management of Special Groups" for details. In children, ciprofloxacin dose should not exceed 1 g/d, chloramphenicol should not exceed 4 g/d. Children younger than 2 years should not receive chloramphenicol.

¶Refer to "Management of Special Groups" for details and for discussion of breastfeeding women. In neonates, gentamicin loading dose of 4 mg/kg should be given initially.[63]

#Duration of treatment of plague in mass casualty setting is 10 days. Duration of postexposure prophylaxis to prevent plague infection is 7 days.

**Children younger than 2 years should not receive chloramphenicol. Oral formulation available only outside the United States.

††Tetracycline could be substituted for doxycycline.

Management of Special Groups

Consensus recommendations for special groups as set forth in the following reflect the clinical and evidence-based judgments of the working group and do not necessarily correspond to FDA approved use, indications, or labeling.

Children. The treatment of choice for plague in children has been streptomycin or gentamicin.[21,40] If aminoglycosides are not available or cannot be used, recommendations for alternative antimicrobial treatment with efficacy against plague are conditioned by balancing risks associated with treatment against those posed by pneumonic plague. Children aged 8 years and older can be treated with tetracycline antibiotics safely.[35,40] However, in children younger than 8 years, tetracycline antibiotics may cause discolored teeth, and rare instances of retarded skeletal growth have been reported in infants.[35] Chloramphenicol is considered safe in children except for children younger than 2 years who are at risk of "gray baby syndrome."[35,40] Some concern exists that fluoroquinolone use in children may cause arthropathy,[35] although fluoroquinolones have been used to treat serious infections in children.[64] No comparative studies assessing efficacy or safety of alternative treatment strategies for plague in children has or can be performed.

Given these considerations, the working group recommends that children in the contained casualty setting receive streptomycin or gentamicin. In a mass casualty setting or for postexposure prophylaxis, we recommend that doxycycline be used. Alternatives are listed for both settings (Table 2). The working group assessment is that the potential benefits of these antimicrobials in the treating of pneumonic plague infection substantially outweigh the risks.

Pregnant Women. It has been recommended that aminoglycosides be avoided in pregnancy unless severe illness warrants,[35,65] but there is no more efficacious treatment for pneumonic plague. Therefore, the working group recommends that pregnant women in the contained casualty setting receive gentamicin (Table 2). Since streptomycin has been associated with rare reports of irreversible deafness in children following fetal exposure, this medication should be avoided if possible.[35] The tetracycline class of antibiotics has been associated with fetal toxicity including retarded skeletal growth,[35] although a large case-control study of doxycycline use in pregnancy showed no significant increase in teratogenic risk to the fetus.[66] Liver toxicity has been reported in pregnant women following large doses of intravenous tetracycline (no longer sold in the United States), but it has also been reported following oral administration of tetracycline to nonpregnant individuals.[35] Balancing the risks of pneumonic plague infection with those associated with doxycycline use in pregnancy, the working group recommends that doxycycline be used to treat pregnant women with pneumonic plague if gentamicin is not available.

Of the oral antibiotics historically used to treat plague, only trimethoprim-sulfamethoxazole has a category C pregnancy classification[65]; however, many experts do not recommend trimethoprim-sulfamethoxazole for treatment of pneumonic plague. Therefore, the working group recommends that pregnant women receive oral doxycycline for mass casualty treatment or postexposure prophylaxis. If the patient is unable to take doxycycline or the medication is unavailable, ciprofloxacin or other fluoroquinolones would be recommended in the mass casualty setting (Table 2).

The working group recommendation for treatment of breastfeeding women is to provide the mother and infant with the same antibiotic based on what is most safe and effective for the infant: gentamicin in the contained casualty setting and doxycycline in the mass casualty setting. Fluoroquinolones would be the recommended alternative (Table 2).

Immunosuppressed Persons. The antibiotic treatment or postexposure prophylaxis for pneumonic plague among those who are immunosuppressed has not been studied in human or animal models of pneumonic plague infection. Therefore, the consensus recommendation is to administer antibiotics according to the guidelines developed for immunocompetent adults and children.

POSTEXPOSURE PROPHYLAXIS RECOMMENDATIONS

The working group recommends that in a community experiencing a pneumonic plague epidemic, all persons developing a temperature of 38.5°C or higher or new cough should promptly begin parenteral antibiotic treatment. If the resources required to administer parenteral antibiotics are unavailable, oral antibiotics should be used according to the mass casualty recommendations (Table 2). For infants in this setting, tachypnea would also be an additional indication for immediate treatment.[29] Special measures would need to be initiated for treatment or prophylaxis of those who are either unaware of the outbreak or require special assistance, such as the homeless or mentally handicapped persons. Continuing surveillance of patients would be needed to identify individuals and communities at risk requiring postexposure prophylaxis.

Asymptomatic persons having household, hospital, or other close contact with persons with untreated pneumonic plague should receive postexposure antibiotic prophylaxis for 7 days[29] and watch for fever and cough. Close contact is defined as contact with a patient at less than 2 meters.[16,31] Tetracycline, doxycycline, sulfonamides, and chloramphenicol have each been used or recommended as postexposure prophylaxis in this setting.[16,22,29,31,59] Fluoroquinolones could also be used based on studies in mice.[51]

The working group recommends the use of doxycycline as the first choice antibiotic for postexposure prophylaxis; other recommended antibiotics are noted (Table 2). Contacts who develop fever or cough while receiving prophylaxis should seek prompt medical attention and begin antibiotic treatment as described in Table 2.

INFECTION CONTROL

Previous public health guidelines have advised strict isolation for all close contacts of patients with pneumonic plague who refuse prophylaxis.[29] In the modern setting, however, pneumonic plague has not spread widely or rapidly in a community,[4,14,24] and therefore isolation of close contacts refusing antibiotic prophylaxis is not recommended by the working group. Instead, persons refusing prophylaxis should be carefully watched for the development of fever or cough during the first 7 days after exposure and treated immediately should either occur.

Modern experience with person-to-person spread of pneumonic plague is limited; few data are available to make specific recommendations regarding appropriate infection control measures. The available evidence indicates that person-to-person transmission of pneumonic plague occurs via respiratory droplets; transmission by droplet nuclei has not been demonstrated.[14-17] In large pneumonic plague epidemics earlier this century, pneumonic plague transmission was prevented in close contacts by wearing masks.[14,16,17] Commensurate with this, existing national infection control guidelines recommend the use of disposable surgical masks to prevent the transmission of pneumonic plague.[29,67]

Given the available evidence, the working group recommends that, in addition to beginning antibiotic prophylaxis, persons living or working in close contact with patients with confirmed or suspect pneumonic plague that have had less than 48 hours of antimicrobial treatment should follow respiratory droplet precautions and wear a surgical mask. Further, the working group recommends avoidance of unnecessary close contact with patients with pneumonic plague until at least 48 hours of antibiotic therapy and clinical improvement has taken place. Other standard respiratory droplet precautions (gown, gloves, and eye protection) should be used as well.[29,31]

The patient should remain isolated during the first 48 hours of antibiotic therapy and until clinical improvement occurs.[29,31,59] If large numbers of patients make individual isolation impossible, patients with pneumonic plague may be cohorted while undergoing antibiotic therapy. Patients being transported should also wear surgical masks. Hospital rooms of patients with pneumonic plague should receive terminal cleaning in a manner consistent with standard precautions, and clothing or linens contaminated with body fluids of patients infected with plague should be disinfected as per hospital protocol.[29]

Microbiology laboratory personnel should be alerted when *Y pestis* is suspected. Four laboratory-acquired cases of plague have been reported in the United States.[68] Simple clinical materials and cultures should be processed in biosafety level 2 conditions.[31,69] Only during activities involving high potential for aerosol or droplet production (eg, centrifuging, grinding, vigorous shaking, and animal studies) are biosafety level 3 conditions necessary.[69]

Bodies of patients who have died following infection with plague should be handled with routine strict precautions.[29] Contact with the remains should be limited to trained personnel, and the safety precautions for transporting corpses for burial should be the same as those when transporting ill patients.[70] Aerosol-generating procedures, such as bone-sawing associated with surgery or postmortem examinations, would be associated with special risks of transmission and are not recommended. If such aerosol-generating procedures are necessary, then high-efficiency particulate air filtered masks and negative-pressure rooms should be used as would be customary in cases in which contagious biological aerosols, such as *Mycobacterium tuberculosis*, are deemed a possible risk.[71]

ENVIRONMENTAL DECONTAMINATION

There is no evidence to suggest that residual plague bacilli pose an environmental threat to the population following the dissolution of the primary aerosol. There is no spore form in the *Y pestis* life cycle, so it is far more susceptible to environmental conditions than sporulating bacteria such as *Bacillus anthracis*. Moreover, *Y pestis* is very sensitive to the action of sunlight and heating and does not survive long outside the host.[72] Although some reports suggest that the bacterium may survive in the soil for some time,[72] there is no evidence to suggest environmental risk to humans in this setting and thus no need for environmental decontamination of an area exposed to an aerosol of plague. In the WHO analysis, in a worst case scenario, a plague aerosol was estimated to be effective and infectious for as long as 1 hour.[7] In the setting of a clandestine release of plague bacilli, the aerosol would have dissipated long before the first case of pneumonic plague occurred.

ADDITIONAL RESEARCH

Improving the medical and public health response to an outbreak of plague following the use of a biological weapon will require additional knowledge of the organism, its genetics, and pathogenesis. In addition, improved rapid diagnostic and standard laboratory microbiology techniques are necessary. An improved understanding of prophylactic and therapeutic antibiotic regimens would be of benefit in defining optimal antibiotic strategy.

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PLACER COUNTY

HEALTH AND HUMAN SERVICES

COMMUNICABLE DISEASE CONTROL

Medical Treatment and Response to Suspected Plague: Information for Health Care Providers During Biologic Emergencies

ALL SUSPECT CASES OF PLAGUE MUST BE REPORTED IMMEDIATELY TO THE PLACER COUNTY HEALTH AND HUMAN SERVICES, COMMUNICABLE DISEASE CONTROL:

During Business Hours: (530) 889-7141

After Hours (Nights, Weekends and Holidays): Health Officer Richard J. Burton, M.D., M.P.H., at (530) 889-7119

(In the event that you are unable to reach a Communicable Disease Control Contact, please call the Placer County Office of Emergency Services at (530) 886-5300 or the 24-hour dispatch at (530) 886-5375).

I. KEY SUMMARY POINTS

- Highly infectious after aerosolization
- Person-to-person and animal-to-human transmission can occur with pneumonic plague via respiratory droplet

Clinical:

- Incubation period is 1-3 days (ranges up to 7 days)
- Aerosolization would most likely result in pneumonic plague
- Pneumonic plague presents with acute onset of high fevers, chills, headache, malaise and a productive cough, that is initially watery before becoming bloody

Laboratory Diagnosis:

- Bacterial cultures (blood, sputum, or lymph node aspirate specimens) should be handled in a Biosafety Level 2 facility
- Wright, Giemsa, or Wayson stain shows gram negative coccobacilli with bipolar “safety-pin” appearance
- Organism grows slowly (48 hrs for observable growth) on standard blood and MacConkey agar
- Immunoflourescent staining for capsule (F1 antigen) is diagnostic

Patient Isolation:

- Strict respiratory isolation with droplet precautions (gown, gloves, and eye protection) until the patient has received at least 48 hours of antibiotic therapy and shows clinical improvement

Treatment:

- Streptomycin (1 g IM bid) or gentamicin (5 mg/kg IM or IV qd) are the preferred antibiotics
- Tetracyclines or flouroquinolones are alternative choices
- Co-trimoxazole is recommended for pregnant women and children between the ages of 2 months and 8 years
- Chloramphenicol should be used for plague meningitis

Prophylaxis:

- Antibiotic prophylaxis is recommended for all persons exposed to the aerosol or persons in close physical contact with a confirmed case
- Tetracyclines or flouroquinolones are recommended for 7 days from last exposure to a case

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II. Introduction/Epidemiology

Plague is transmitted by a gram-negative bacillus, *Yersinia pestis*, of the family Enterobacteriaceae. Plague is a zoonosis and can be transmitted by flea vectors from rodents to humans, and by respiratory droplets from animals to humans and humans to humans. Plague has three clinical forms: bubonic, primary septicemic and pneumonic disease. **Primary pneumonic plague would be the most likely presentation in the event of a biological attack.**

Naturally-occurring plague is a disease primarily affecting rodents. Transmission between rodents is via infected fleas. Transmission to humans can occur by respiratory droplets from rodents, from other infected animals/materials to humans or from human to human. In the United States, transmission to humans has been primarily from the bites of fleas from infected rodents. Less frequently, infection is caused by direct contact with body fluids or tissues while handling an infected animal. Currently in the United States, infected cats are the only source of primary pneumonic plague for humans, since persons who develop secondary plague pneumonia usually receive appropriate isolation and treatment before secondary transmission can occur.

Human plague has been reported most often from the four western states of New Mexico, Arizona, Colorado and California. In the United States, 341 cases of human plague were reported during 1970-1995; the overwhelming majority of cases were bubonic plague.

Since primary pneumonic plague can be transmitted from person to person, patients with compatible clinical symptoms should be placed in respiratory isolation.

III. Significance as a Potential Bioterrorist Agent

- Could be released as an aerosol during a bioterrorist attack

- Has been weaponized by both the United States, former Soviet Union and Japan. Japan purportedly released plague over China during World War II.

- Potential for secondary transmission is highest with pneumonic plague.

- Aerosolized plague would cause pneumonic disease, with high mortality rates if untreated.

IV. Clinical Manifestations

During an act of bioterrorism, release of an aerosol will be the most likely method of dispersal, so that most patients will present with primary pneumonic plague.

A. Primary Pneumonic Plague

Incubation period - typically 1-3 days (ranges up to 7 days)

Symptoms - Patients exhibit acute and often fulminant onset of high fever, malaise, headache, myalgias and cough with production of sputum that is initially watery, before becoming bloody. Pneumonia rapidly progresses to dyspnea, stridor and cyanosis. Patients may develop respiratory failure, shock and ecchymoses.

B. Primary Septicemic Plague

Incubation period - 1-7 days

Symptoms - Clinically resembles septicemia caused by other gram negative bacteria. Patients are febrile and often have chills, headache, malaise and gastrointestinal disturbances. May progress rapidly to septic shock, consumptive coagulopathy, meningitis and coma. Patients may develop secondary plague pneumonia.

C. Bubonic Plague

Incubation period - 2-7 days

Symptoms - Patients develop fever, headache, chills and swollen, extremely painful lymph nodes (buboes). Nausea, vomiting and diarrhea are common. Swollen nodes typically involve the nodes that drain the site of initial infection. Patients generally do not have overlying skin lesions. Patients may develop secondary septicemic plague or secondary plague pneumonia.

V. Laboratory Diagnosis

Laboratory work must be done in Biosafety Level 2 facilities. If plague is suspected, please call the Placer County Public Health Laboratory at (530) 889-7205 to arrange for submission of specimens for testing and/or confirmation at the state Microbial Diseases Laboratory. After hours, please call Placer County Health Officer Richard J. Burton, M.D., M.P.H.,at (530) 889-7119.

The diagnosis of plague may be suspected based on characteristic findings on microscopic staining of appropriate body fluids and confirmed by immunofluorescent staining for the capsule or bacterial culture. Serology is generally used retrospectively to confirm suspect cases.

- **Staining of Specimens**
  - Appropriate clinical specimens include: blood, bubo aspirates, sputum, CSF (if signs/symptoms of meningitis) and skin scrapings (if a lesion is present).
  - **Gram stain**: polymorphonuclear leukocytes and bipolar staining, "safety-pin" ovoid, gram-negative cocco-bacilli identified in bubo aspirate, sputum or CSF are highly suggestive of plague.
  - **Wayson stain**: *Yersinia pestis* appears as light blue bacilli with dark blue polar bodies on a contrasting pink ground.
  - **Immunofluorescent staining of capsule (F1)**: A positive finding is diagnostic. Must use fresh specimens to avoid false negatives. This test is available only at reference laboratories.
- **Bacterial cultures**

  Blood, bubo aspirates, sputum, CSF and skin scrapings can be cultured.

  Materials should be inoculated into blood and MacConkey agar plates and infusion broth. It generally takes 2 days to identify visible colonies. Rapid biochemical

identification systems may not be reliable for identification due to slower growth rate of *Y. pestis.*

- **Serologic Testing**

  Several serologic tests are available including a passive hemagglutination test (CDC). A fourfold or greater rise is diagnostic, a single titre of > 1:16 in someone without prior immunization against plague is suggestive. Serology is not useful for rapid diagnosis.

VI. Handling Laboratory Specimens

Laboratory staff handling specimens from persons who are suspected of having plague should follow Biosafety Level 2 precautions. Staff must wear surgical gloves, protective gowns and shoe covers. Laboratory tests should be performed in Biological Safety Level 2 cabinets, and blood cultures should be maintained in a closed system. Every effort should be made to avoid splashing or creating an aerosol, and protective eye wear and masks should be worn if work cannot be done in a Biological Safety Level 2 cabinet.

Laboratories working with a large amount of organism or doing studies on antibiotic resistant strains should use Biological Safety Level 3 cabinets. A full-face mask respirator with a HEPA (high efficiency particulate air) filter is an acceptable but cumbersome alternative to masks and protective eye wear.

Accidental spills of potentially contaminated material should be decontaminated immediately by covering liberally with a disinfectant solution (0.1% sodium hypochlorite or sodium hydroxide (0.1N)). All biohazardous waste should be decontaminated by autoclaving. Contaminated equipment or instruments may be decontaminated with a hypochlorite solution, hydrogen peroxide, peracetic acid, 1% glutaraldehyde solution, formaldehyde, ethylene oxide, copper irradiation, or other O.S.H.A. approved solutions, or by autoclaving or boiling for 10 minutes.

VII. Treatment

Supportive care combined with the rapid administration of parenteral antibiotics are the keys to successful management of plague. Plague pneumonia is almost always fatal if antibiotics are not begun within 24 hours of onset of symptoms.

- **Recommended Antibiotics**

  The drug of choice for primary pneumonic plague is **streptomycin** [30 mg /kg/day administered by intramuscular injection every 12 hours (15 mg/kg) for 10 days].

However, since streptomycin may be in short supply, **Gentamicin** [1.7 mg/kg every 8 hours intravenously or intramuscularly for 10 days] and **doxycycline** [200mg intravenous loading dose, followed by 100mg IV every 12 hours for 10-14 days] are alternative agents.

Chloramphenicol should be used for plague meningitis due to its better CNS penetration [loading dose of 25 mg/kg intravenously followed by 50-75 mg/kg/day divided into four equal doses; continue for 10 days after clinical improvement].

Antibiotic choice may need to be altered as susceptibility information becomes available.

- **Alternative Antibiotics**

  Ciprofloxacin [400 mg intravenously every 12 hours], **Levofloxacin** [500 mg intravenously every 24 hours], and **Ofloxacin** [400 mg orally every 12 hours] are acceptable alternative agents. The efficacy of quinolones in humans has not been formally evaluated.

  Bactrim [1 double-strength tablet orally every 12 hours or its intravenous equivalent] may also be efficacious based on animal and in vitro studies.

  Much less effective drugs (**do not use** unless all other alternatives are unavailable) include: rifampin, aztreonam, ampicillin, ceftazadime, cefotetan and cefazolin.

- **Supportive therapy** - Supportive care is essential, including intravenous fluids and hemodynamic monitoring.

- **Therapy in pediatric patients**

  First-line agents: **streptomycin** [15 mg/kg intramuscularly every 12 hours] or **gentamicin** [1.7 mg/kg intramuscularly or intravenously every 8 hours].

  Alternatively: **If > or = 8 years of age** - **Doxycycline** [100 mg intravenously or orally every 12 hours if > 45 kg; 2.2mg/kg intravenously or orally every 12 hours if < 45 kg],

  If < 8 years of age - **Co-trimoxazole** [4 mg/kg orally or intravenously every 12 hours].

- Newborns up to age 2 months, **ciprofloxacin** 10-20 mg/kg intravenously or orally twice daily, do not exceed 1 gram/day.

- **Therapy in pregnant women** - Avoid streptomycin in pregnancy due to its association with irreversible deafness in children exposed in utero. Gentamicin can be used (1.7 mg/kg every 8 hours). **Bactrim DS [1 tablet twice daily or its I.V. equivalent] is the preferred therapy for pregnant women, except at term, when a fluoroquinolone** (Ciprofloxacin 500 orally or intravenously every 12 hours) **is preferred**. If worsening illness, add a tetracycline agent as the benefits outweigh the risks. (NOTE: Liver function tests should be monitored due to potential hepatotoxicity with tetracycline use during pregnancy.)

VIII. Isolation of Patients

Pneumonic plague can be spread from person-to-person by droplet transmission (coughing, sneezing). All staff should observe **Standard Precautions** when caring for patients with suspected or confirmed plague. Patients with **pneumonic plague** should be placed on **strict respiratory isolation with Droplet Precautions until 48 hours of appropriate antibiotics** have been administered AND the patient is showing clinical improvement. Droplet precautions require that the patient be placed in a private room and that persons entering the patient room wear a surgical mask, especially when within three feet of the patient. *Negative pressure rooms are not indicated*. Transmission can occur from plague skin lesions (such as draining buboes or abscesses) to contacts; wound and skin precautions should be followed if skin lesions are present.

Multiple patients with pneumonic plague may be cohorted as long as all patients are receiving appropriate therapy.

IX. Disposal of Infectious Waste

Use of tracking forms, containment, storage, packaging, treatment and disposal methods should be based upon the same rules as all other regulated medical wastes.

X. Autopsy and Handling of Corpses

All postmortem procedures are to be performed using Universal Precautions. Efforts should be made to avoid aerosolization.

- All persons performing or assisting in postmortem procedures must wear mandated P.P.E. (personal protective equipment) as delineated by O.S.H.A. guidelines.

- Instruments should be autoclaved or sterilized with a 10% bleach solution or other solutions approved by O.S.H.A. Surfaces contaminated during postmortem procedures should be decontaminated with an appropriate chemical germicide such as 10% hypochlorite or 5% phenol (carbolic acid).

XI. Management of Exposed Persons

An exposed person is defined as a person who has been exposed to aerosolized *Yersinia pestis* or has been in close physical contact with a confirmed case-patient (contact at less than 2 meters during a period when the case was symptomatic and before the case had received 48 hours of antibiotic therapy). Household contacts and healthcare worker contacts should be considered exposed and should receive prophylaxis.

Antibiotics: **All antibiotic therapy should continue for 7 days from *last exposure* to the case. Decisions on antibiotic therapy should be based on susceptibility results.**

Non-pregnant Adult Post-Exposure Prophylaxis

Tetracycline 500 mg every 6 hours, orally
Doxycycline 100 mg every 12 hours, orally
Ciprofloxacin 500 mg every 12 hours, orally
Ofloxacin 400 mg every 12 hours, orally
Levofloxacin 500 mg every 24 hours, orally

Alternative Therapy
Trimethoprim/sulfamethoxazole 40 mg/kg/day in 2 equal doses at 12 hour intervals, orally.

Pediatric Post-Exposure Prophylaxis - Co-trimoxazole is the preferred antibiotic, or when benefits outweigh the risks, consider use of doxycycline or fluoroquinolones.

If > or = 8 years of age:	**Doxycycline:**	If > or = 45 kg - 100 mg orally every 12 hours If < 45 kg - 2.2 mg/kg orally every 12 hours
If < 8 years of age:	**Co-trimoxazole**	4 mg/kg orally every 12 hours
	Chloramphenicol	25 mg/kg orally every 12 hours
Newborns up to age 2 months:	**Ciprofloxacin**	10-20 mg/kg orally twice daily, do not exceed 1 gram/day.

Pregnant Women Post-Exposure Prophylaxis - Co-trimoxazole [1 DS tablet orally twice daily], is the preferred antibiotic, except at term, when the risk of kernicteris is greatest -- use fluoroquinolones [ciprofloxacin 500 mg orally twice daily]

XII. Reporting to the Health Department

Plague is a reportable disease in California. *All suspect cases* should be immediately reported by telephone:

I. **During business hours**

Placer County Health and Human Services, Communicable Disease Control at (530)-889-7141

II. After business hours

Health Officer Richard J. Burton, M.D., M.P.H., at (530) 889-7119

III. In the event that you are unable to reach a Communicable Disease Control Contact, please call the Placer County Office of Emergency Services at (530) 886-5300 or the 24-hour dispatch at (530) 886-5375

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BOTULISM

ALL SUSPECT CASES OF BOTULISM MUST BE REPORTED IMMEDIATELY TO THE HEALTH AND HUMAN SERVICES COMMUNICABLE DISEASE CONTROL:

During business hours: (530) 889-7141
After hours (Health Officer Richard J. Burton, M.D., M.P.H.): (530) 889-7119

(In the event that you are unable to reach a Communicable Disease Control Contact, please call the Placer County Office of Emergency Services at (530) 886-5300 during business hours, or 24-hour dispatch at (530) 886-5375 after business hours.)

Epidemiology:

- Botulism neurotoxins (A-F) could be transmitted by aerosol or contamination of food and water supplies
- **Botulism is not transmitted from person to person**

Clinical:

- Incubation period is 12-36 hours (can be several days)
- Early symptoms include blurred vision, diplopia, and dry mouth
- Later symptoms include dysarthria, dysphagia, dysphonia, ptosis and the development of a symmetrical, descending progressive paralysis and respiratory failure
- Patients are usually alert and afebrile

Laboratory Diagnosis:

- Diagnosis is primarily based on a compatible clinical presentation
- Spinal protein is normal and characteristic findings are seen on EMG (facilitation of the compound muscle action potential on repetitive nerve stimulation)
- Toxin can be detected in serum (collect 30 cc in red top) and stool (foodborne botulism) by mouse neutralization bioassay performed at California Microbial Diseases Laboratory.
- Contact the Placer County Public Health Laboratory for assistance.

Patient Isolation:

- Standard precautions. Patients do not require isolation rooms.

Treatment:

- Supportive care is the mainstay of therapy; prolonged ventilatory support is often required in severe cases
- Botulism anti-toxin (for A, B and E toxins) is in limited supply and is available only from the Division of Communicable Disease Control, California Dept of Health Services. Contact Placer County Communicable Disease Control for assistance.

Prophylaxis:

- Currently, there is no available post-exposure prophylaxis

Botulinum Toxin as a Biological Weapon
Medical and Public Health Management

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Kevin Tonat, PhD, MPH
for the Working Group on Civilian Biodefense

Objective The Working Group on Civilian Biodefense has developed consensus-based recommendations for measures to be taken by medical and public health professionals if botulinum toxin is used as a biological weapon against a civilian population.

Participants The working group included 23 representatives from academic, government, and private institutions with expertise in public health, emergency management, and clinical medicine.

Evidence The primary authors (S.S.A. and R.S.) searched OLDMEDLINE and MEDLINE (1960–March 1999) and their professional collections for literature concerning use of botulinum toxin as a bioweapon. The literature was reviewed, and opinions were sought from the working group and other experts on diagnosis and management of botulism. Additional MEDLINE searches were conducted through April 2000 during the review and revisions of the consensus statement.

Consensus Process The first draft of the working group's consensus statement was a synthesis of information obtained in the formal evidence-gathering process. The working group convened to review the first draft in May 1999. Working group members reviewed subsequent drafts and suggested additional revisions. The final statement incorporates all relevant evidence obtained in the literature search in conjunction with final consensus recommendations supported by all working group members.

Conclusions An aerosolized or foodborne botulinum toxin weapon would cause acute symmetric, descending flaccid paralysis with prominent bulbar palsies such as diplopia, dysarthria, dysphonia, and dysphagia that would typically present 12 to 72 hours after exposure. Effective response to a deliberate release of botulinum toxin will depend on timely clinical diagnosis, case reporting, and epidemiological investigation. Persons potentially exposed to botulinum toxin should be closely observed, and those with signs of botulism require prompt treatment with antitoxin and supportive care that may include assisted ventilation for weeks or months. Treatment with antitoxin should not be delayed for microbiological testing.

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THIS IS THE FOURTH ARTICLE IN A series entitled *Medical and Public Health Management Following the Use of a Biological Weapon: Consensus Statements of The Working Group on Civilian Biodefense*.[1-3] This article is the only one in the series to feature a biological toxin rather than a replicating agent. Botulinum toxin poses a major bioweapon threat because of its extreme potency and lethality; its ease of production, transport, and misuse; and the need for prolonged intensive care among affected persons.[4,5] An outbreak of botulism constitutes a medical emergency that requires prompt provision of botulinum antitoxin and, often, mechanical ventilation, and it constitutes a public health emergency that requires immediate intervention to prevent additional cases. Timely recognition of a botulism outbreak begins with an astute clinician who quickly notifies public health officials.

Botulinum toxin is the most poisonous substance known.[6,7] A single gram of crystalline toxin, evenly dispersed and inhaled, would kill more than 1 million people, although technical factors would make such dissemination difficult. The basis of the phenomenal potency of botulinum toxin is enzymatic; the toxin is a zinc proteinase that cleaves 1 or more of the fusion proteins by which neuronal vesicles release acetylcholine into the neuromuscular junction.[8]

It is regrettable that botulinum toxin still needs to be considered as a bioweapon at the historic moment when it has become the first biological toxin to become licensed for treatment of human disease. In the United States, botulinum toxin is currently licensed for treatment of cervical torticollis, strabismus, and blepharospasm associ-

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ated with dystonia. It is also used "off label" for a variety of more prevalent conditions that include migraine headache, chronic low back pain, stroke, traumatic brain injury, cerebral palsy, achalasia, and various dystonias.[9-13]

CONSENSUS METHODS

The working group included 23 representatives from academic, government, and private institutions with expertise in public health, emergency management, and clinical medicine. The 2 primary authors (S.S.A. and R.S.) conducted a literature search on use of botulinum toxin as a bioweapon. The OLDMEDLINE and MEDLINE databases were queried for all articles published between January 1960 and March 1999 that contained words referring to biological warfare (*bioterrorism*, *biowarfare*, *terrorism*, *war*, *warfare*, and *weapon*) in combination with terms related to *Clostridium botulinum* (*bacillus*, *botulin*, *botulinal*, *botulinum*, *botulinus*, *botulism*, *clostridia*, *clostridial*, and *Clostridium*). The articles identified in the databases were fully reviewed. In addition, published and unpublished articles, books, monographs, and special reports in the primary authors' collections were reviewed. Additional MEDLINE searches were conducted through April 2000 during the review and revisions of the consensus statement.

The first draft of the consensus statement was a synthesis of information obtained in the formal evidence-gathering process. Members of the working group provided written and oral comments about the first draft at their meeting in May 1999. Working group members then reviewed subsequent drafts and suggested additional revisions. The final statement incorporates all relevant evidence obtained in the literature search in conjunction with final consensus recommendations supported by all working group members.

The assessment and recommendations provided herein represent the best professional judgment of the working group based on currently available data and expertise. These conclusions and recommendations should be regularly reassessed as new information becomes available.

HISTORY OF CURRENT THREAT

Terrorists have already attempted to use botulinum toxin as a bioweapon. Aerosols were dispersed at multiple sites in downtown Tokyo, Japan, and at US military installations in Japan on at least 3 occasions between 1990 and 1995 by the Japanese cult Aum Shinrikyō. These attacks failed, apparently because of faulty microbiological technique, deficient aerosol-generating equipment, or internal sabotage. The perpetrators obtained their *C botulinum* from soil that they had collected in northern Japan.[14,15]

Development and use of botulinum toxin as a possible bioweapon began at least 60 years ago.[16,17] The head of the Japanese biological warfare group (Unit 731) admitted to feeding cultures of *C botulinum* to prisoners with lethal effect during that country's occupation of Manchuria, which began in the 1930s.[18] The US biological weapons program first produced botulinum toxin during World War II. Because of concerns that Germany had weaponized botulinum toxin, more than 1 million doses of botulinum toxoid vaccine were made for Allied troops preparing to invade Normandy on D-Day.[19,20] The US biological weapons program was ended in 1969-1970 by executive orders of Richard M. Nixon, then president. Research pertaining to biowarfare use of botulinum toxin took place in other countries as well.[21]

Although the 1972 Biological and Toxin Weapons Convention prohibited offensive research and production of biological weapons, signatories Iraq and the Soviet Union subsequently produced botulinum toxin for use as a weapon.[22,23] Botulinum toxin was 1 of several agents tested at the Soviet site Aralsk-7 on Vozrozhdeniye Island in the Aral Sea.[23,24] A former senior scientist of the Russian civilian bioweapons program reported that the Soviets had attempted splicing the botulinum toxin gene from *C botulinum* into other bacteria.[25] With the economic difficulties in Russia after the demise of the Soviet Union, some of the thousands of scientists formerly employed by its bioweapons program have been recruited by nations attempting to develop biological weapons.[25,26] Four of the countries listed by the US government as "state sponsors of terrorism" (Iran, Iraq, North Korea, and Syria)[27] have developed, or are believed to be developing, botulinum toxin as a weapon.[28,29]

After the 1991 Persian Gulf War, Iraq admitted to the United Nations inspection team to having produced 19 000 L of concentrated botulinum toxin, of which approximately 10 000 L were loaded into military weapons.[22,30] These 19 000 L of concentrated toxin are not fully accounted for and constitute approximately 3 times the amount needed to kill the entire current human population by inhalation. In 1990, Iraq deployed specially designed missiles with a 600-km range; 13 of these were filled with botulinum toxin, 10 with aflatoxin, and 2 with anthrax spores. Iraq also deployed special 400-lb (180-kg) bombs for immediate use; 100 bombs contained botulinum toxin, 50 contained anthrax spores, and 7 contained aflatoxin.[22,30] It is noteworthy that Iraq chose to weaponize more botulinum toxin than any other of its known biological agents.

Some contemporary analyses discount the potential of botulinum toxin as a bioweapon because of constraints in concentrating and stabilizing the toxin for aerosol dissemination. However, these analyses pertain to military uses of botulinum toxin to immobilize an opponent (William C. Patrick, unpublished data, 1998). In contrast, deliberate release of botulinum toxin in a civilian population would be able to cause substantial disruption and distress. For example, it is estimated that a point-source aerosol release of botulinum toxin could incapacitate or kill 10% of persons within 0.5 km downwind (William C. Patrick, unpublished data, 1998). In addition, terrorist use of botulinum toxin might be manifested as deliberate contamination of food. Misuse of toxin in this manner could produce either a large

botulism outbreak from a single meal or episodic, widely separated outbreaks.[31] In the United States, the Centers for Disease Control and Prevention (CDC) maintains a well-established surveillance system for human botulism based on clinician reporting that would promptly detect such events.[32]

MICROBIOLOGY AND VIRULENCE FACTORS

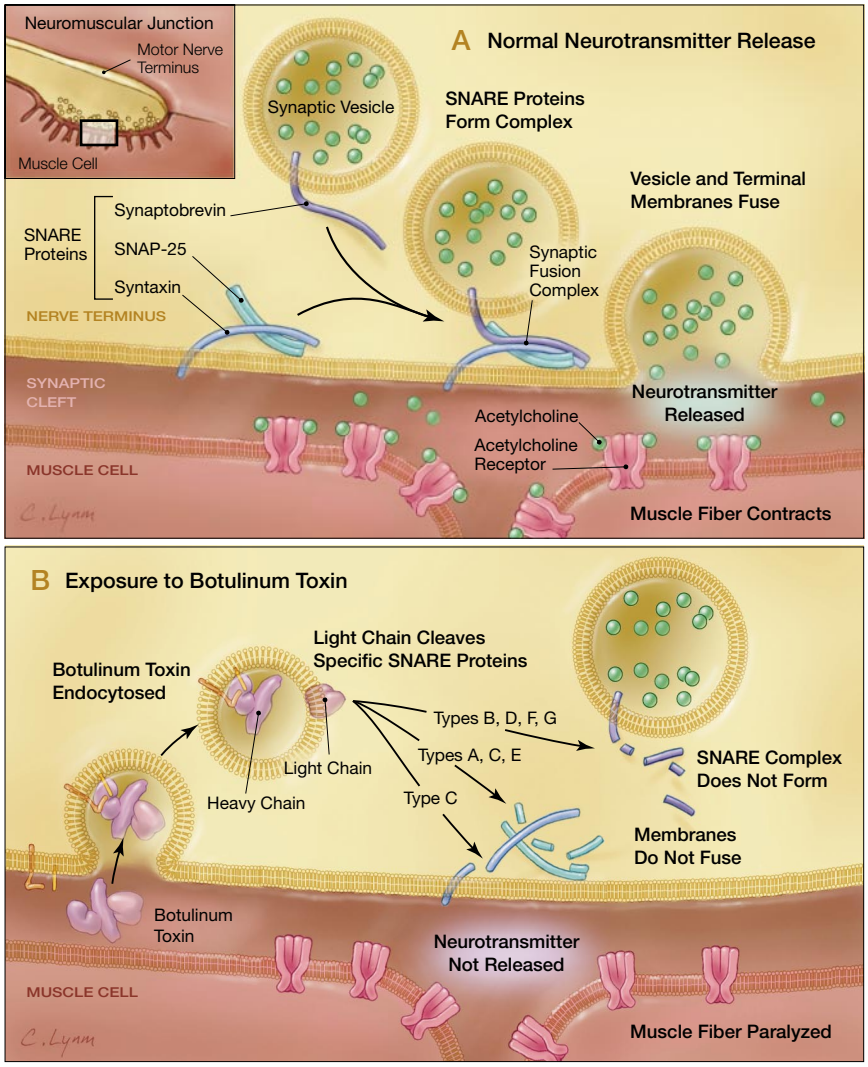
Clostridium botulinum is a spore-forming, obligate anaerobe whose natural habitat is soil, from which it can be isolated without undue difficulty. The species *C botulinum* consists of 4 genetically diverse groups that would not otherwise be designated as a single species except for their common characteristic of producing botulinum toxin.[33,34] Botulinum toxin exists in 7 distinct antigenic types that have been assigned the letters A through G. The toxin types are defined by their absence of cross-neutralization (eg, anti-A antitoxin does not neutralize toxin types B-G). The toxin types also serve as convenient epidemiological markers. In addition to *C botulinum*, unique strains of *Clostridium baratii* and *Clostridium butyricum* have the capacity to produce botulinum toxin.[35-37] Botulinum toxin is a simple dichain polypeptide that consists of a 100-kd "heavy" chain joined by a single disulfide bond to a 50-kd "light" chain; its 3-dimensional structure was recently resolved to 3.3 A.[38] The toxin's light chain is a Zn^{++}-containing endopeptidase that blocks acetylcholine-containing vesicles from fusing with the terminal membrane of the motor neuron, resulting in flaccid muscle paralysis (FIGURE 1).[8]

The lethal dose of botulinum toxin for humans is not known but can be estimated from primate studies. By extrapolation, the lethal amounts of crystalline type A toxin for a 70-kg human would be approximately 0.09-0.15 µg intravenously or intramuscularly, 0.70-0.90 µg inhalationally, and 70 µg orally.[10,39-41] Therapeutic botulinum toxin represents an impractical bioterrorist weapon because a vial of the type A preparation currently licensed in the United States contains only about 0.3% of the estimated human lethal inhalational dose and 0.005% of the estimated lethal oral dose.

PATHOGENESIS AND CLINICAL MANIFESTATIONS

Three forms of naturally occurring human botulism exist: foodborne, wound, and intestinal (infant and adult). Fewer than 200 cases of all forms of botulism are reported annually in the United States.[42] All forms of botulism result from absorption of botulinum toxin into the circulation from either a mucosal surface (gut, lung) or a wound. Botulinum toxin does not penetrate intact skin. Wound botulism and intestinal

Figure 1. Mechanism of Action of Botulinum Toxin

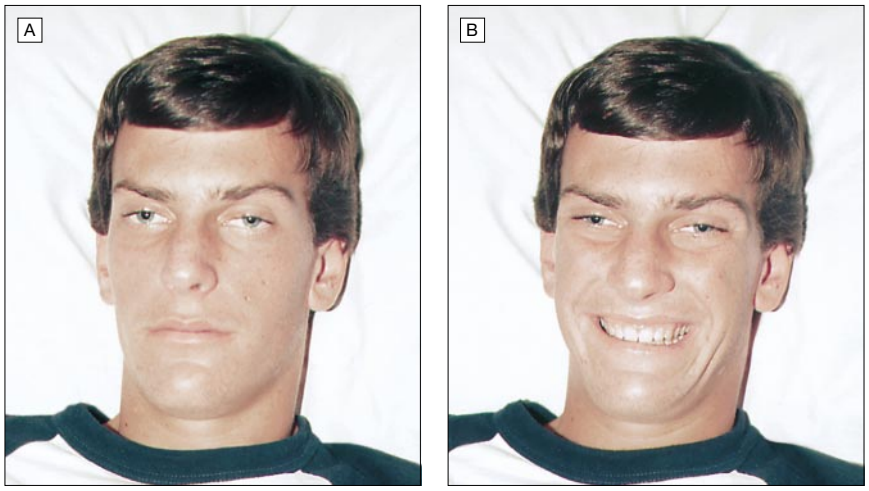


A, Release of acetylcholine at the neuromuscular junction is mediated by the assembly of a synaptic fusion complex that allows the membrane of the synaptic vesicle containing acetylcholine to fuse with the neuronal cell membrane. The synaptic fusion complex is a set of SNARE proteins, which include synaptobrevin, SNAP-25, and syntaxin. After membrane fusion, acetylcholine is released into the synaptic cleft and then bound by receptors on the muscle cell.

B, Botulinum toxin binds to the neuronal cell membrane at the nerve terminus and enters the neuron by endocytosis. The light chain of botulinum toxin cleaves specific sites on the SNARE proteins, preventing complete assembly of the synaptic fusion complex and thereby blocking acetylcholine release. Botulinum toxins types B, D, F, and G cleave synaptobrevin; types A, C, and E cleave SNAP-25; and type C cleaves syntaxin. Without acetylcholine release, the muscle is unable to contract.

SNARE indicates soluble NSF-attachment protein receptor; NSF, N-ethylmaleimide-sensitive fusion protein; and SNAP-25, synaptosomal-associated protein of 25 kd.

Figure 2. Seventeen-Year-Old Patient With Mild Botulism



A, Patient at rest. Note bilateral mild ptosis, dilated pupils, disconjugate gaze, and symmetric facial muscles. B, Patient was requested to perform his maximum smile. Note absent periorbital smile creases, ptosis, disconjugate gaze, dilated pupils, and minimally asymmetric smile. As an indication of the extreme potency of botulinum toxin, the patient had 40×10^{-12}g/mL of type A botulinum toxin in his serum (ie, 1.25 mouse units/mL) when these photographs were taken.

botulism are infectious diseases that result from production of botulinum toxin by *C botulinum* either in devitalized (ie, anaerobic) tissue[43] or in the intestinal lumen,[37] respectively. Neither would result from bioterrorist use of botulinum toxin.

A fourth, man-made form that results from aerosolized botulinum toxin is inhalational botulism. This mode of transmission has been demonstrated experimentally in primates,[39] has been attempted by bioterrorists,[14,15] and has been the intended outcome of at least 1 country's specially designed missiles and artillery shells.[22,30] Inhalational botulism has occurred accidentally in humans. A brief report from West Germany in 1962 described 3 veterinary personnel who were exposed to reaerosolized botulinum toxin while disposing of rabbits and guinea pigs whose fur was coated with aerosolized type A botulinum toxin. Type A botulinum toxin was detected in serum samples from all 3 affected individuals.[21]

Once botulinum toxin is absorbed, the bloodstream carries it to peripheral cholinergic synapses, principally, the neuromuscular junction, where it binds irreversibly. The toxin is then internalized and enzymatically blocks acetylcholine release (Figure 1). Accordingly, all forms of human botulism display virtually identical neurologic signs. However, the neurologic signs in naturally occurring foodborne botulism may be preceded by abdominal cramps, nausea, vomiting, or diarrhea.[44] These gastrointestinal symptoms are thought to be caused by other bacterial metabolites also present in the food[33] and may not occur if purified botulinum toxin is intentionally placed in foods or aerosols.

Botulism is an acute, afebrile, symmetric, descending flaccid paralysis that always begins in bulbar musculature. It is not possible to have botulism without having multiple cranial nerve palsies. Disease manifestations are similar regardless of botulinum toxin type. However, the extent and pace of paralysis may vary considerably among patients. Some patients may be mildly affected (FIGURE 2), while others may be so paralyzed that they appear comatose and require months of ventilatory support. The rapidity of onset and the severity of paralysis depend on the amount of toxin absorbed into the circulation. Recovery results from new motor axon twigs that sprout to reinnervate paralyzed muscle fibers, a process that, in adults, may take weeks or months to complete.[45,46]

Table 1. Symptoms and Signs of Foodborne Botulism, Types A and B*

	Cases, %
Symptoms	
Fatigue	77
Dizziness	51
Double vision	91
Blurred vision	65
Dysphagia	96
Dry mouth	93
Dysarthria	84
Sore throat	54
Dyspnea	60
Constipation	73
Nausea	64
Vomiting	59
Abdominal cramps	42
Diarrhea	19
Arm weakness	73
Leg weakness	69
Paresthesia	14
Signs	
Alert mental status	90
Ptosis	73
Gaze paralysis	65
Pupils dilated or fixed	44
Nystagmus	22
Facial palsy	63
Diminished gag reflex	65
Tongue weakness	58
Arm weakness	75
Leg weakness	69
Hyporeflexia or areflexia	40
Ataxia	17

*Data are from outbreaks of botulism reported in the United States in 1973-1974. The number of patients with available data varied from 35 to 55. Adapted from Hughes et al[44] with permission.

Patients with botulism typically present with difficulty seeing, speaking, and/or swallowing (TABLE 1 and TABLE 2). Prominent neurologic findings in all forms of botulism include ptosis, diplopia, blurred vision, often enlarged or sluggishly reactive pupils, dysarthria, dysphonia, and dysphagia.[5,44,47,48] The mouth may appear dry and the pharynx injected because of peripheral parasympathetic cholinergic blockade. Sensory changes are not observed except for infrequent circumoral and peripheral paresthesias from hyperventilation as a patient becomes frightened by onset of paralysis.

As paralysis extends beyond bulbar musculature, loss of head control, hy-

potonia, and generalized weakness become prominent. Dysphagia and loss of the protective gag reflex may require intubation and, usually, mechanical ventilation. Deep tendon reflexes may be present initially but diminish or disappear in the ensuing days, and constipation may occur. In untreated persons, death results from airway obstruction (pharyngeal and upper airway muscle paralysis) and inadequate tidal volume (diaphragmatic and accessory respiratory muscle paralysis).

Because botulism is an intoxication, patients remain afebrile unless they also have acquired a secondary infection (eg, aspiration pneumonia). The toxin does not penetrate brain parenchyma, so patients are not confused or obtunded. However, they often appear lethargic and have communication difficulties because of bulbar palsies (Figure 2). Botulism may be recognized by its classic triad: (1) symmetric, descending flaccid paralysis with prominent bulbar palsies in (2) an afebrile patient with (3) a clear sensorium. The prominent bulbar palsies can be summarized in part as "4 Ds": diplopia, dysarthria, dysphonia, and dysphagia.

Table 2. Symptoms and Signs of Inhalational Botulism in Order of Onset

Humans (n = 3)[21]	Monkeys (n = 9)[39]*
Third day after exposure	12-18 hours after exposure
Mucus in throat	Mild muscular weakness
Difficulty swallowing solid food	Intermittent ptosis
Dizziness	Disconjugate gaze
Fourth day after exposure	Followed by
Difficulty moving eyes	Severe weakness of postural neck muscles
Mild pupillary dilation and nystagmus	Occasional mouth breathing
Indistinct speech	Serous nasal discharge
Unsteady gait	Salivation, dysphagia
Extreme weakness	Mouth breathing
	Rales
	Anorexia
	Severe generalized weakness
	Lateral recumbency
	Second to fourth day after exposure
	Death in some animals

*After exposure to 4 to 7 monkey median lethal doses of botulinum toxin. The time to onset and pace of paralysis were dose-dependent. Adapted from Middlebrook and Franz[48] with permission.

EPIDEMIOLOGY

Early recognition of outbreaks of botulism, whether natural or intentional, depends on heightened clinical suspicion. Aerosol dissemination may not be difficult to recognize because a large number of cases will share a common temporal and geographical exposure and will lack a common dietary exposure. However, identification of the common exposure site initially may be difficult because of the mobility of persons exposed during the incubation period. Botulism and botulinum toxin are not contagious and cannot be transmitted from person to person. In contrast, a microbe intentionally modified to produce botulinum toxin might be contagious.

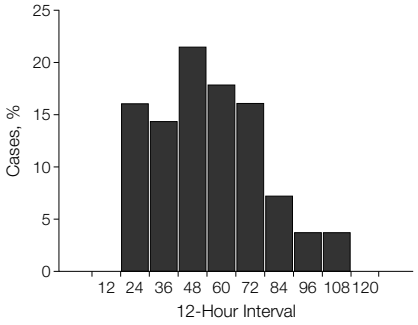
No instances of waterborne botulism have ever been reported.[42,49,50] Although the potency of botulinum toxin has led to speculation that it might be used to contaminate a municipal water supply, this scenario is unlikely for at least 2 reasons.[51] First, botulinum toxin is rapidly inactivated by standard potable water treatments (eg, chlorination, aeration).[52] Second, because of the slow turnover time of large-capacity reservoirs, a comparably large (and technically difficult to produce and deliver) inoculum of botulinum toxin would be needed.[53] In contrast with treated water, botulinum toxin may be stable for several days in untreated water or beverages.[52,54] Hence, such items should be investigated in a botulism outbreak if no other vehicle for toxin can be identified.

If food were deliberately used as a vehicle for the toxin, the outbreak would need to be distinguished from naturally occurring foodborne botulism. During the past 20 years, the epidemiology of foodborne botulism has expanded beyond its traditional association with home-preserved foods and now includes nonpreserved foods and public eating places,[47] features that could make terrorist use of botulinum toxin more difficult to detect. Characteristics of outbreaks of botulism include:

Incubation Period

The rapidity of onset and severity of botulism depend on the rate and amount of toxin absorption. Symptoms of foodborne botulism may begin as early as 2 hours or as long as 8 days after ingestion of toxin.[55,56] Typically, cases present 12 to 72 hours after the implicated meal. In 1 large foodborne outbreak, new cases presented during the ensuing 3 days at a fairly even rate before decreasing (FIGURE 3).[57] The time to onset of inhalational botulism cannot be stated with certainty because so few cases are known. Monkeys showed signs of botulism 12 to 80 hours after aerosol exposure to 4 to 7 multiples of the monkey median lethal dose.[39] The 3 known human cases of inhalational botulism had

Figure 3. Fifty-Nine Cases of Botulism, by Interval Between Eating at a Restaurant and Onset of First Neurologic Symptom—Michigan, 1977



Reproduced from Terranova et al[57] with permission of Oxford University Press.

Box 1. Features of an Outbreak That Would Suggest a Deliberate Release of Botulinum Toxin

Outbreak of a large number of cases of acute flaccid paralysis with prominent bulbar palsies

Outbreak with an unusual botulinum toxin type (ie, type C, D, F, or G, or type E toxin not acquired from an aquatic food)

Outbreak with a common geographic factor among cases (eg, airport, work location) but without a common dietary exposure (ie, features suggestive of an aerosol attack)

Multiple simultaneous outbreaks with no common source

Note: A careful travel and activity history, as well as dietary history, should be taken in any suspected botulism outbreak. Patients should also be asked if they know of other persons with similar symptoms.

onset of symptoms approximately 72 hours after exposure to an unknown but probably small amount of reaerosolized toxin.[21]

Age and Sex

Persons of all ages are potentially susceptible to botulism. There are no sex differences in susceptibility.

Agent and Vehicles

Botulinum toxin in solution is colorless, odorless, and, as far as is known, tasteless. The toxin is readily inactivated by heat (≥85°C for 5 minutes).[33,34,52] Thus, foodborne botulism is always transmitted by foods that are not heated, or not heated thoroughly, before eating. Almost every type of food has been associated with outbreaks of botulism, but the most commonly implicated foods in the United States are vegetables, particularly "low-acid" (ie, higher pH) vegetables such as beans, peppers, carrots, and corn.[42,50,58]

A novel epidemiological development is the occurrence of foodborne botulism after eating various nonpreserved foods in restaurants or delicatessens. Foil-wrapped baked potatoes are now known to be capable of causing restaurant-associated foodborne botulism[59] when held at room temperature after baking and then served plain,[60] as potato salad,[61,62] or as a Mediterranean-style dip.[59] Other outbreaks that originated in restaurants resulted from contaminated condiments such as sautéed onions,[63] garlic in oil,[64] and commercial cheese sauce.[65] Additional examples of notable commercial foods that have caused botulism outbreaks include inadequately eviscerated fish,[66] yogurt,[67] cream cheese,[68] and jarred peanuts.[69]

Incidence and Outbreak Size

Naturally occurring foodborne botulism is a rare disease. Approximately 9 outbreaks of foodborne botulism and a median of 24 cases occur annually in the United States.[42,47] The mean outbreak size has remained constant over the years at approximately 2.5 cases per outbreak. The largest outbreak of foodborne botulism in the United States in the last 100 years occurred in Michigan in 1977; 59 cases resulted from eating home-preserved jalapeño peppers at a restaurant.[57] However, only 45 of the 59 patients had clinically evident weakness and hypotonia.

Toxin Types

Of the 135 foodborne outbreaks in the 16 years from 1980 to 1996 in the United States, the toxin types represented were: type A, 54.1%; type B, 14.8%; type E, 26.7%; type F, 1.5%; and unknown, 3.0%.[42] Type F foodborne outbreaks are rare in the United States; a 1962 outbreak resulted from homemade venison jerky,[70] while other type F cases actually may have had intestinal botulism.[71] Toxin types C and D cause botulism in wildlife and domestic animals but have not caused human foodborne disease. However, humans are thought to be susceptible to these toxin types because they have caused botulism in primates when ingested.[72-74] Toxin type G is produced by a bacteria species discovered in South American soil in 1969 that has never caused recognized foodborne botulism.[75] Aerosol challenge studies in monkeys have established the susceptibility of primates to inhaled botulinum toxin types C, D, and G.[48]

Distribution

Although outbreaks of foodborne botulism have occurred in almost all states, more than half (53.8%) of the US outbreaks have occurred in just 5 western states (California, Washington, Oregon, Colorado, and Alaska). East of the Mississippi River, 60% of the foodborne outbreaks have resulted from type B toxin, while west of the Mississippi River, 85% have resulted from type A toxin. In the 46 years between 1950 and 1996, 20 states, mainly in the eastern United States, did not report any type A botulism outbreaks, while 24 states, mostly in the western United States, did not report any type B outbreaks.[42] In Canada and Alaska, most foodborne outbreaks resulted from type E toxin associated with native Inuit and Eskimo foods.[50,76]

Bioterrorism Considerations

Any outbreak of botulism should bring to mind the possibility of bioterrorism, but certain features would be particularly suggestive (BOX 1). The availability and speed of air transportation mandate that a careful travel and activity history, as well as a careful dietary history, be taken. Patients should also be asked whether they know of other persons with similar symptoms. Absence of a common dietary exposure among temporally clustered patients should suggest the possibility of inhalational botulism.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Clinical diagnosis of botulism is confirmed by specialized laboratory test-

ing that often requires days to complete. Routine laboratory test results are usually unremarkable. Therefore, clinical diagnosis is the foundation for early recognition of and response to a bioterrorist attack with botulinum toxin.

Any case of suspected botulism represents a potential public health emergency because of the possibility that a contaminated food remains available to others or that botulinum toxin has been deliberately released. In these settings, prompt intervention by civil authorities is needed to prevent additional cases. Consequently, clinicians caring for patients with suspected botulism should notify their local public health department and hospital epidemiologist immediately to coordinate shipment of therapeutic antitoxin, laboratory diagnostic testing, and epidemiological investigation (BOX 2). In most jurisdictions of the United States, botulism suspected on clinical grounds alone by law must be reported immediately by telephone to local public health authorities. The attending clinician needs to be both prompt and persistent in accomplishing this notification.

Box 2. Clinicians Caring for Patients With Suspected Botulism Should Immediately Contact Their:

(1) Hospital epidemiologist or infection control practitioner

and

(2) Local and state health departments

Consult your local telephone operator; the telephone directory under "government listings," or the Internet at: http://www.cdc.gov/other.htm#states or http://www.astho.org/state.html

If the local and state health departments are unavailable, contact the Centers for Disease Control and Prevention: (404) 639-2206; (404) 639-2888 [after hours].

Differential Diagnosis

Botulism is frequently misdiagnosed, most often as a polyradiculoneuropathy (Guillain-Barré or Miller-Fisher syndrome), myasthenia gravis, or a disease of the central nervous system (TABLE 3). In the United States, botulism is more likely than Guillain-Barré syndrome, intoxication, or poliomyelitis to cause a cluster of cases of acute flaccid paralysis. Botulism differs from other flaccid paralyses in its prominent cranial nerve palsies disproportionate to milder weakness and hypotonia below the neck, in its symmetry, and in its absence of sensory nerve damage.

A large, unintentional outbreak of foodborne botulism caused by a restaurant condiment in Canada provides a cautionary lesson about the potential difficulties in recognizing a covert, intentional contamination of food.[64] During a 6-week period in which the condiment was served, 28 persons in 2 countries became ill, but all were misdiagnosed (Table 3). The 28 were identified retrospectively only after correct diagnoses in a mother and her 2 daughters who had returned to their home more than 2000 miles away from the restaurant. Four (14%) of the cases had been misdiagnosed as having psychiatric disease, including "factitious" symptoms. It is possible that hysterical paralysis might occur as a conversion reaction in the anxiety that would

Table 3. Selected Mimics and Misdiagnoses of Botulism*

Conditions	Features That Distinguish Condition From Botulism
Common Misdiagnoses	
Guillain-Barré syndrome† and its variants, especially Miller-Fisher syndrome	History of antecedent infection; paresthesias; often ascending paralysis; early areflexia; eventual CSF protein increase; EMG findings
Myasthenia gravis†	Recurrent paralysis; EMG findings; sustained response to anticholinesterase therapy
Stroke†	Paralysis often asymmetric; abnormal CNS image
Intoxication with depressants (eg, acute ethanol intoxication), organophosphates, carbon monoxide, or nerve gas	History of exposure; excessive drug levels detected in body fluids
Lambert-Eaton syndrome	Increased strength with sustained contraction; evidence of lung carcinoma; EMG findings similar to botulism
Tick paralysis	Paresthesias; ascending paralysis; tick attached to skin
Other Misdiagnoses	
Poliomyelitis	Antecedent febrile illness; asymmetric paralysis; CSF pleocytosis
CNS infections, especially of the brainstem	Mental status changes; CSF and EEG abnormalities
CNS tumor	Paralysis often asymmetric; abnormal CNS image
Streptococcal pharyngitis (pharyngeal erythema can occur in botulism)	Absence of bulbar palsies; positive rapid antigen test result or throat culture
Psychiatric illness†	Normal EMG in conversion paralysis
Viral syndrome†	Absence of bulbar palsies and flaccid paralysis
Inflammatory myopathy†	Elevated creatine kinase levels
Diabetic complications†	Sensory neuropathy; few cranial nerve palsies
Hyperemesis gravidarum†	Absence of bulbar palsies and acute flaccid paralysis
Hypothyroidism†	Abnormal thyroid function test results
Laryngeal trauma†	Absence of flaccid paralysis; dysphonia without bulbar palsies
Overexertion†	Absence of bulbar palsies and acute flaccid paralysis

*CSF indicates cerebrospinal fluid; EMG, electromyogram; CNS, central nervous system; and EEG, electroencephalogram.
†Misdiagnoses made in a large outbreak of botulism.[64]

follow a deliberate release of botulinum toxin.

Diagnostic Testing

At present, laboratory diagnostic testing for botulism in the United States is available only at the CDC and approximately 20 state and municipal public health laboratories.[42] The laboratory should be consulted prospectively about specimen collection and processing. Samples used in diagnosis of botulism include serum (≥30 mL of blood in "tiger"-top or red-top tubes from adults, less from children), stool, gastric aspirate, and, if available, vomitus and suspect foods. Serum samples must be obtained before therapy with antitoxin, which nullifies the diagnostic mouse bioassay. An enema may be required to obtain an adequate fecal sample if the patient is constipated. Sterile water should be used for this procedure because saline enema solution can confound the mouse bioassay. Gastric aspirates and, perhaps, stool may be useful for detecting inhaled aerosolized botulinum toxin released in a bioterrorist attack.[77] A list of the patient's medications should accompany the diagnostic samples because anticholinesterases, such as pyridostigmine bromide, and other medicines that are toxic to mice can be dialyzed from samples before testing. All samples should be kept refrigerated after collection.

The standard laboratory diagnostic test for clinical specimens and foods is the mouse bioassay,[42] in which type-specific antitoxin protects mice against any botulinum toxin present in the sample. The mouse bioassay can detect as little as 0.03 ng of botulinum toxin[10] and usually yields results in 1 to 2 days (range, 6-96 hours). Fecal and gastric specimens also are cultured anaerobically, with results typically available in 7 to 10 days (range, 5-21 days). Toxin production by culture isolates is confirmed by the mouse bioassay.

An electromyogram with repetitive nerve stimulation at 20 to 50 Hz can sometimes distinguish between causes of acute flaccid paralysis.[78,79] The characteristic electromyographic findings of botulism include normal nerve conduction velocity, normal sensory nerve function, a pattern of brief, small-amplitude motor potentials, and, most distinctively, an incremental response (facilitation) to repetitive stimulation often seen only at 50 Hz. Immediate access to electrophysiological studies may be difficult to obtain in an outbreak of botulism.

Additional diagnostic procedures may be useful in rapidly excluding botulism as the cause of paralysis (Table 3). Cerebrospinal fluid (CSF) is unchanged in botulism but is abnormal in many central nervous system diseases. Although the CSF protein level eventually is elevated in Guillain-Barré syndrome, it may be normal early in illness. Imaging of the brain, spine, and chest may reveal hemorrhage, inflammation, or neoplasm. A test dose of edrophonium chloride briefly reverses paralytic symptoms in many patients with myasthenia gravis and, reportedly, in some with botulism.[64] A close inspection of the skin, especially the scalp, may reveal an attached tick that is causing paralysis.[80] Other tests that require days for results include stool culture for *Campylobacter jejuni* as a precipitant of Guillain-Barré syndrome and assays for the autoantibodies that cause myasthenia gravis, Lambert-Eaton syndrome, and Guillain-Barré syndrome.

Foods suspected of being contaminated should be refrigerated until retrieval by public health personnel. The US Food and Drug Administration and the US Department of Agriculture can assist other public health laboratories with testing of suspect foods by using methods similar to those applied to clinical samples.

THERAPY

The mortality and sequelae associated with botulism have diminished with contemporary therapy. In the United States, the percentage of persons who died of foodborne botulism decreased from 25% during 1950-1959 to 6% during 1990-1996, with a similar reduction for each botulinum toxin type.[42] Despite this increase in survival, the paralysis of botulism can persist for weeks to months with concurrent requirements for fluid and nutritional support, assisted ventilation, and treatment of complications.

Therapy for botulism consists of supportive care and passive immunization with equine antitoxin. Optimal use of botulinum antitoxin requires early suspicion of botulism. Timely administration of passive neutralizing antibody will minimize subsequent nerve damage and severity of disease but will not reverse existent paralysis.[81,82] Antitoxin should be given to patients with neurologic signs of botulism as soon as possible after clinical diagnosis.[47] Treatment should not be delayed for microbiological testing. Antitoxin may be withheld at the time of diagnosis if it is certain that the patient is improving from maximal paralysis.

In the United States, botulinum antitoxin is available from the CDC via state and local health departments (Box 2). The licensed trivalent antitoxin contains neutralizing antibodies against botulinum toxin types A, B, and E, the most common causes of human botulism. If another toxin type was intentionally disseminated, patients could potentially be treated with an investigational heptavalent (ABCDEFG) antitoxin held by the US Army.[83] However, the time required for correct toxin typing and subsequent administration of heptavalent antitoxin would decrease the utility of this product in an outbreak.

The dose and safety precautions for equine botulinum antitoxin have changed over time. Clinicians should review the package insert with public health authorities before using antitoxin. At present, the dose of licensed botulinum antitoxin is a single 10-mL vial per patient, diluted 1:10 in 0.9% saline solution, administered by slow intravenous infusion. One vial provides between 5500 and 8500 IU of each type-specific antitoxin. The amount of neutralizing antibody in both the licensed and the investigational equine antitoxins far exceeds the highest serum toxin levels found in foodborne botu-

lism patients, and additional doses are usually not required. If a patient has been exposed to an unnaturally large amount of botulinum toxin as a biological weapon, the adequacy of neutralization by antitoxin can be confirmed by retesting serum for toxin after treatment.

There are few published data on the safety of botulinum antitoxins. From 1967 to 1977, when the recommended dose was larger than today, approximately 9% of recipients of equine botulinum antitoxin in the United States displayed urticaria, serum sickness, or other reactions suggestive of hypersensitivity.[84] Anaphylaxis occurred within 10 minutes of receiving antitoxin in 2% of recipients. When the US Army's investigational heptavalent antitoxin was given to 50 individuals in a large Egyptian outbreak of type E foodborne botulism in 1991, 1 recipient (2%) displayed serum sickness, and 9 (18%) had mild reactions.[83] To screen for hypersensitivity, patients are given small challenge doses of equine antitoxin before receiving a full dose. Patients responding to challenge with a substantial wheal and flare may be desensitized over 3 to 4 hours before additional antitoxin is given. During the infusion of antitoxin, diphenhydramine and epinephrine should be on hand for rapid administration in case of adverse reaction. Although both equine antitoxins have been partially despeciated by enzymatic cleavage of the allogenic F_c region, each contains a small residual of intact antibody that may sensitize recipients to additional doses.

Botulism patients require supportive care that often includes feeding by enteral tube or parenteral nutrition, intensive care, mechanical ventilation, and treatment of secondary infections. Patients with suspected botulism should be closely monitored for impending respiratory failure. In nonventilated infants with botulism, a reverse Trendelenburg positioning with cervical vertebral support has been helpful, but applicability of this positioning to adults with botulism remains untested. This tilted, flat-body positioning with neck support may improve ventilation by reducing entry of oral secretions into the airway and by suspending more of the weight of the abdominal viscera from the diaphragm, thereby improving respiratory excursion (FIGURE 4). In contrast, placing a botulism patient in a supine or semirecumbent position (trunk flexed 45° at the waist) may impede respiratory excursion and airway clearance, especially if the patient is obese. The desired angle of the reverse Trendelenburg position is 20° to 25°.

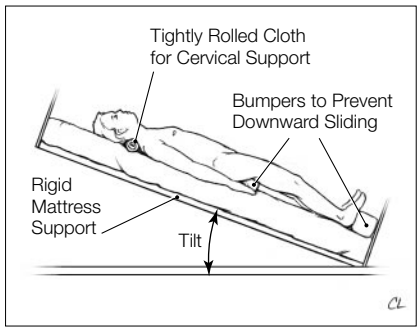
Botulism patients should be assessed for adequacy of gag and cough reflexes, control of oropharyngeal secretions, oxygen saturation, vital capacity, and inspiratory force. Airway obstruction or aspiration usually precedes hypoventilation in botulism. When respiratory function deteriorates, controlled, anticipatory intubation is indicated. The proportion of patients with botulism who require mechanical ventilation has varied from 20% in a foodborne outbreak[64] to more than 60% in infant botulism.[85] In a large outbreak of botulism, the need for mechanical ventilators, critical care beds, and skilled personnel might quickly exceed local capacity and persist for weeks or months. Development of a reserve stockpile of mechanical ventilators in the United States is under way[86] and will require a complement of staff trained in their use.

Antibiotics have no known direct effect on botulinum toxin. However, secondary infections acquired during botulism often require antibiotic therapy. Aminoglycoside antibiotics and clindamycin are contraindicated because of their ability to exacerbate neuromuscular blockade.[87,88] Standard treatments for detoxification, such as activated charcoal,[89] may be given before antitoxin becomes available, but there are no data regarding their effectiveness in human botulism.

SPECIAL POPULATIONS

Based on limited information, there is no indication that treatment of children, pregnant women, and immunocompromised persons with botulism should differ from standard therapy.

Figure 4. Preferred Positioning of Nonventilated Botulism Patients



Note flat, rigid mattress tilted at 20°, tightly rolled cloth to support cervical vertebrae, and bumpers to prevent downward sliding. Use of this position may postpone or avoid the need for mechanical ventilation in mildly affected patients because of improved respiratory mechanics and airway protection.

Despite the risks of immediate hypersensitivity and sensitization to equine proteins, both children[43,90] and pregnant women[91,92] have received equine antitoxin without apparent short-term adverse effects. The risks to fetuses of exposure to equine antitoxin are unknown. Treatment with human-derived neutralizing antibody would decrease the risk of allergic reactions posed by equine botulinum antitoxin, but use of the investigational product, Botulism Immune Globulin Intravenous (Human) (California Department of Health Services, Berkeley), is limited to suspected cases of infant botulism.[82,93]

PROPHYLAXIS

Botulism can be prevented by the presence of neutralizing antibody in the bloodstream. Passive immunity can be provided by equine botulinum antitoxin or by specific human hyperimmune globulin, while endogenous immunity can be induced by immunization with botulinum toxoid.

Use of antitoxin for postexposure prophylaxis is limited by its scarcity and its reactogenicity. Because of the risks of equine antitoxin therapy, it is less certain how best to care for persons who may have been exposed to botulinum toxin but who are not yet ill. In a small

study of primates exposed to aerosolized toxin in which supportive care was not provided, all 7 monkeys given antitoxin after exposure but before the appearance of neurologic signs survived, while 2 of 4 monkeys treated with antitoxin only after the appearance of neurologic signs died.[39] Moreover, all monkeys infused with neutralizing antibody before exposure to toxin displayed no signs of botulism. In a balance between avoiding the potential adverse effects of equine antitoxin and needing to rapidly neutralize toxin, it is current practice in foodborne botulism outbreaks to closely monitor persons who may have been exposed to botulinum toxin and to treat them promptly with antitoxin at the first signs of illness.[47] To facilitate distribution of scarce antitoxin following the intentional use of botulinum toxin, asymptomatic persons who are believed to have been exposed should remain under close medical observation and, if feasible, near critical care services.

In the United States, an investigational pentavalent (ABCDE) botulinum toxoid is distributed by the CDC for laboratory workers at high risk of exposure to botulinum toxin and by the military for protection of troops against attack.[94] A recombinant vaccine is also in development.[95] The pentavalent toxoid has been used for more than 30 years to immunize more than 3000 laboratory workers in many countries. Immunization of the population with botulinum toxoid could in theory eliminate the hazard posed by botulinum toxins A through E. However, mass immunization is neither feasible nor desirable for reasons that include scarcity of the toxoid, rarity of natural disease, and elimination of the potential therapeutic benefits of medicinal botulinum toxin. Accordingly, preexposure immunization currently is neither recommended for nor available to the general population. Botulinum toxoid induces immunity over several months and, so, is ineffective as postexposure prophylaxis.

DECONTAMINATION

Despite its extreme potency, botulinum toxin is easily destroyed. Heating to an internal temperature of 85°C for at least 5 minutes will detoxify contaminated food or drink.[52] All foods suspected of contamination should be promptly removed from potential consumers and submitted to public health authorities for testing.

Persistence of aerosolized botulinum toxin at a site of deliberate release is determined by atmospheric conditions and the particle size of the aerosol. Extremes of temperature and humidity will degrade the toxin, while fine aerosols will eventually dissipate into the atmosphere. Depending on the weather, aerosolized toxin has been estimated to decay at between less than 1% to 4% per minute.[96] At a decay rate of 1% per minute, substantial inactivation (≥13 logs) of toxin occurs by 2 days after aerosolization.

Recognition of a covert release of finely aerosolized botulinum toxin would probably occur too late to prevent additional exposures. When exposure is anticipated, some protection may be conferred by covering the mouth and nose with clothing such as an undershirt, shirt, scarf, or handkerchief.[97] In contrast with mucosal surfaces, intact skin is impermeable to botulinum toxin.

After exposure to botulinum toxin, clothing and skin should be washed with soap and water.[98] Contaminated objects or surfaces should be cleaned with 0.1% hypochlorite bleach solution if they cannot be avoided for the hours to days required for natural degradation.[33,52,98]

INFECTION CONTROL

Medical personnel caring for patients with suspected botulism should use standard precautions. Patients with suspected botulism do not need to be isolated, but those with flaccid paralysis from suspected meningitis require droplet precautions.

RESEARCH NEEDS

Additional research in diagnosis and treatment of botulism is required to minimize its threat as a weapon. Rapid diagnostic and toxin typing techniques currently under development would be useful for recognizing and responding to a bioterrorist attack. Although polymerase chain reaction assays can detect the botulinum toxin gene,[99] they are unable, as yet, to determine whether the toxin gene is expressed and whether the expressed protein is indeed toxic. Assays that exploit the enzymatic activity of botulinum toxin have the potential to supplant the mouse bioassay as the standard for diagnosis.[100] Detection of botulinum toxin in aerosols by enzyme-linked immunosorbent assay[101] is a component of the US military's Biological Integrated Detection System for rapid recognition of biological agents in the battlefield.[17]

The distribution of botulinum antitoxin to local hospitals from regional depots takes several hours. In contrast, standard detoxification techniques can be applied immediately. Studies are needed to assess whether activated charcoal and osmotic catharsis can prevent gastrointestinal tract absorption or reduce circulating levels of botulinum toxin. Enteral detoxification may be less useful in inhalational botulism than in foodborne disease.

The competing needs for immunity to weaponized botulinum toxin and for susceptibility to medicinal botulinum toxin could be reconciled by supplying human antibody that neutralizes toxin. With a half-life of approximately 1 month,[102] human antibody would provide immunity for long periods and avoid the reactogenicity of equine products. Existing in vitro technologies could produce the stockpiles of fully human antibody necessary both to deter terrorist attacks and to avoid the rationing of antitoxin that currently would be required in a large outbreak of botulism.[103-106] A single small injection of oligoclonal human antibodies could, in theory, provide protection against toxins A through G for many months. Until such a product becomes available, the possibilities for reducing the population's vulnerability to the intentional misuse of botulinum toxin remain limited.

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Disclaimers: In some instances, the indications, dosages, and other information in this article are not consistent with current approved labeling by the US Food and Drug Administration (FDA). The recommendations on use of drugs and vaccine for uses not approved by the FDA do not represent the official views of the FDA nor of any of the federal agencies whose scientists participated in these discussions. Unlabeled uses of the products recommended are noted in the sections of this article in which these products are discussed. Where unlabeled uses are indicated, information used as the basis for the recommendation is discussed.

The views, opinions, assertions, and findings contained herein are those of the authors and should not be construed as official US Department of Defense or US Department of Army positions, policies, or decisions unless so designated by other documentation.

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current national point prevalence data are available. In addition, there are no quantitative data suggesting isotretinoin misuse, and the informed consent specifically indicates that the patient has been diagnosed with the FDA-approved indication. It is important to note that Roche Laboratories promotes the use of isotretinoin exclusively for patients with this approved indication.

Finally, it is important to state that the clinical criteria for the use of this drug in an individual patient must be left to the judgment of the physician, who is the only appropriate person to define the treatment plan for that patient.

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RESEARCH LETTER

Persistent Pain in Nursing Home Residents

To the Editor: More than 1.5 million people in the United States reside in nursing homes and an estimated 43% of adults 65 years and older will enter a nursing home prior to death.[1] Previous research using an early version of the Minimum Data Set (MDS), a nationally mandated nursing home resident assessment instrument, noted that daily pain was prevalent among nursing home residents diagnosed with cancer who had been discharged from a hospital, as well as among the residents of nursing homes in general.[2] Prior research was restricted by a limited MDS pain frequency measure of "none" or "daily," but since 1998, information on both frequency (none, daily, or less than daily) and severity of pain (mild, moderate, or excruciating at times) has been collected. We report the rates of persistent severe pain among US nursing home residents by analyzing a national repository of MDS data, which represents all nursing home residents in all 50 states.

Methods. We determined the rate of persistent severe pain among all 2.2 million residents of US nursing homes within 60 days of April 1, 1999. The term "persistent pain" indicates residents with pain at an assessment around that time who were also reported to be in daily moderate or excruciating pain at a second assessment, 60 to 180 days later. Using state as the unit of analysis, we adjusted observed rates of persistent severe pain for the nursing home discharge rate and the prevalence of severe pain among all 1999 admissions.

Results. Nationwide, 14.7% of residents in a nursing home for 2 assessments were in persistent pain and 41.2% of residents in pain at first assessment were in severe pain 60 to 180 days later. This rate varied from 37.7% (Mississippi) to 49.5% (Utah). Forty-one states had rates of persistent pain between 39.5% and 46.1%. Individual state reports are available online at http://www.chcr.brown.edu/dying/factsondying.htm.

Comment. We believe that these results underestimate the true pain burden experienced by nursing home residents because the data were reported by nursing home staff rather than by patients. States in which pain is not adequately assessed may report lower rates of persistent pain. Although facilities in states with higher rates of reported pain may be doing a better job of recognizing pain, nearly half of these residents were apparently not afforded adequate palliation. The high rate of persistent pain is consistent with previous research noting that pain is often not appropriately treated in nursing home residents.[2,3] Untreated pain results in impaired mobility, depression, and diminishes quality of life.[3-5] These population results indicate that pain control represents an often neglected need of this vulnerable population.

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CORRECTION

Incorrect Wording and Web Site Address: In the Consensus Statement entitled "Botulinum Toxin as a Biological Weapon: Medical and Public Health Management" published in the February 28, 2001, issue of THE JOURNAL (2001;285:1059-1070), 3 errors appeared. In the third introductory paragraph on page 1059, the word "biological" should be "microbial." In the paragraph labeled "Toxin Types" on page 1064, the word "bacteria" should be "bacterial." Finally, on page 1069, the Web site address for reference 27 should be http://www.state.gov/www/global/terrorism/1999report/1999index.html.

PLACER COUNTY
HEALTH AND HUMAN SERVICES
COMMUNICABLE DISEASE CONTROL

Medical Treatment and Response to Suspected Botulism: Information for Health Care Providers During Biologic Emergencies

ALL SUSPECT CASES OF BOTULISM MUST BE REPORTED IMMEDIATELY TOTHE PLACER COUNTY HEALTH AND HUMAN SERVICES, COMMUNICABLE DISEASE CONTROL:

During Business Hours: (530) 889-7141

After Hours (Nights, Weekends and Holidays): Health Officer Richard J. Burton, M.D., M.P.H., at (530) 889-7119

(In the event that you are unable to reach a Communicable Disease Control Contact, please call the Placer County Office of Emergency Services at (530) 886-5300 or the 24-hour dispatch at (530) 886-5375).

I. KEY SUMMARY POINTS

- Botulism neurotoxins (A-F) could be transmitted by aerosol or contamination of food and water supplies
- **Botulism is <u>not</u> transmitted from person to person**

Clinical:

- Incubation period is 12-36 hours (can be several days)
- Early symptoms include blurred vision, diplopia, and dry mouth
- Later symptoms include dysarthria, dysphagia, dysphonia, ptosis and the development of a symmetrical, descending progressive paralysis and respiratory failure
- Patients are usually alert and afebrile

Laboratory Diagnosis:

- Diagnosis is primarily based on a compatible clinical presentation
- Spinal protein is normal and characteristic findings are seen on EMG (facilitation of the compound muscle action potential on repetitive nerve stimulation)
- Toxin can be detected in serum (collect 30 cc in red top) and stool (foodborne botulism) by mouse neutralization bioassay performed at California Microbial Diseases Laboratory. Contact the Placer County Public Health Laboratory at (530) 889-7205 for assistance.

Patient Isolation:

- Standard precautions. Patients do <u>not</u> require isolation rooms.

Treatment:

- Supportive care is the mainstay of therapy; prolonged ventilatory support is often required in severe cases
- Botulism anti-toxin is in limited supply and is available only from the Division of Communicable Disease Control, California Dept of Health Services

Prophylaxis:

- Currently, there is no available post-exposure prophylaxis

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II. Introduction/Epidemiology

Botulism is a neuroparalytic disease caused by a neurotoxin produced by the anaerobic spore-forming bacterium, *Clostridium botulinum*. Two additional bacteria, *Clostridium barati* and *Clostridium butyricum,* can also occasionally produce botulinum toxin. Botulinum toxins are designated A through G based on antigenic differences. Human botulism is caused by toxin types A, B, E and rarely, F; botulism associated with toxin type A is most severe. In the eastern United States, botulism is primarily caused by the botulinum toxin type B. Botulism is classically acquired by the ingestion of preformed neurotoxin, although botulism can also be caused by localized infection with *C. botulinum* (wound botulism) or *C. botulinum* colonization of the intestine with in vivo toxin production (infant botulism).

Botulinum neurotoxins irreversibly bind to presynaptic receptors of peripheral nerves and subsequently inhibit release of acetylcholine. Both the neuromuscular junctions and cholinergic autonomic synapses are affected, resulting in skeletal muscle and bulbar paralysis. Recovery can take weeks to months, requiring the regeneration of presynaptic axons and formation of new synapses.

Botulism in the United States is now most commonly recognized as wound botulism, which develops as a complication of injecting drug use. Botulism can also present in small clusters or single cases related to home-canned foods or vegetables of low acidity (*e.g., beans, peppers, carrots and corns)*. Recent examples of foodborne botulism due to non-preserved foods include foil-wrapped baked potatoes and sauteed onions. Foodborne botulism is always transmitted by foods that are not heated thoroughly before eating. In 1999, there were 26 cases of foodborne botulism and 41 cases of wound botulism reported in the U.S. Thirty eight of the 41 wound botulism cases were reported in California.

Airborne transmission of botulinum neurotoxin does not usually occur naturally, although three persons were infected by aerosolized toxin while disposing of rabbits and guinea pigs whose fur had been coated with previously aerosolized botulinum toxin during a laboratory accident in Germany in 1962. If used in a bioterrorist attack, aerosolization of preformed toxin would likely occur causing disease by the inhalation route. The clinical manifestations of disease would be identical to foodborne botulism, except for the absence of prodromal gastrointestinal symptoms. Deliberate contamination of food or water supplies is also possible.

Botulism is not transmitted by human-to-human contact.

An outbreak of botulism with the following characteristics should raise suspicion of a bioterrorist attack:

- An unusual toxin type for California
- Multiple, simultaneous cases with no common food exposure, no wounds, and no history of injecting drug use
- Absence of gastrointestinal prodromal symptoms would suggest an aerosolized route of exposure in patients with a clinical presentation compatible with botulism

Significance as a Potential Bioterrorist Agent

- Botulinum toxin is one of the most potent compounds known; it is 100,000 times more toxic than sarin.
- Could be released as an aerosol or used to contaminate water or food supplies.
- Iraq deployed 12,000 liters of botulinum toxin in over 100 munitions during the Gulf War in 1991.
- The Aum Shinrikyo cult released botulinum toxin during a failed bioterrorist attack in Japan.
- A massive outbreak of botulism would easily overwhelm both the existing supply of botulinum antitoxin and intensive care support (ventilator) capacity at acute care hospitals.

III. Clinical Manifestations

During an act of bioterrorism, release of an aerosol will be the most likely route of transmission. The clinical presentation would be similar for both the inhalational and

foodborne routes of transmission, with the exception that inhalational botulism would not have prominent gastrointestinal prodromal symptoms.

Incubation period - typically 12-36 hours, can be several days (dose-dependent). Inhalational botulism may have an incubation period up to 3 days.

Symptoms - Patients may exhibit some or all of the following signs or symptoms: These findings may appear in any order, the following represents the classical temporal relationship:

Early Symptoms (Cranial nerve abnormalities precede peripheral muscle weakness):

- blurred vision
- diplopia (double vision)
- dry mouth

Later Symptoms (more severe disease):

- dysphonia (hoarse voice)
- dysarthria (difficulty articulating words)
- dysphagia (difficulty swallowing)
- ptosis
- symmetrical, descending, progressive muscular weakness with fatiguability with repetitive muscle activity
- respiratory failure

The patient may have dilated or fixed pupils. Patients are typically alert and responsive and sensory deficits (other than blurred vision) do not occur. Deep tendon reflexes may be symmetrically depressed or remain normal. Fever does not occur unless there is a complicating infection.

The differential diagnosis of botulism includes myasthenia gravis and Lambert-Eaton myasthenic syndrome (lack autonomic features), tick paralysis (tick should be attached), acute inflammatory polyneuropathy (Guillain-Barre syndrome {GBS} usually begins with sensory complaints, rarely begins with cranial nerve abnormalities, and the progression of motor weakness may be ascending as opposed to the descending progression seen with botulism {except for the Miller-Fisher variant}; in addition, the CSF protein is usually

elevated in GBS, although it may take 1 – 2 weeks to see an increase), polio (febrile illness with asymmetric weakness), magnesium intoxication and brain stem infarction.

The diagnosis of botulism requires a very high index of suspicion, and is most often based on epidemiologic evidence of a potential exposure. In the event of a bioterrorist attack, a recognized source of exposure may be absent. Clinical suspicion is of utmost importance**.**

IV. Diagnosis

A. Laboratory

Laboratory diagnosis is made by mouse neutralization assay, which is performed only at the California Microbial Diseases Laboratory. If botulism is suspected, please call the Placer County Public Health Laboratory at (530) 889-7205 to arrange for submission of specimens for testing. After hours call Health Officer Richard J. Burton, M.D., M.P.H., at (530) 889-7119.

The diagnosis of botulism requires a compatible clinical syndrome. The detection of botulinum neurotoxin in the patient's serum and/or stool (in the case of food-borne botulism) serves to confirm the diagnosis. The detection of toxin will be dependent on the total dose absorbed and the time from onset of symptoms to testing. The specimens will be evaluated by mouse neutralization bioassay, currently the gold standard assay. This assay can detect as little as 0.03 ng of botulinum toxin.

- Processing of Specimens

  - Obtain serum (draw 30 cc in a tube with no anticoagulant, refrigerate until well-clotted, centrifuge and separate the serum into a sterile tube for transport), stool (at least 25 gm), and gastric aspirate if available. Immediately call the Public Health Laboratory at (530) 889-7205 (after hours call Health Officer Richard J. Burton, M.D., M.P.H., (530)-889-7119).

  - Serum specimens must be taken *before* antitoxin treatment to demonstrate the presence of botulinum toxin.

  - In California, anti-toxin and laboratory testing for toxin are available only from the state Department of Health Services. The Placer County Public Health Laboratory facilitates routing of laboratory specimens. Placer County Communicable Disease Control facilitates evaluation of need for anti-toxin.

- All specimens should be refrigerated, and not frozen, and examined as quickly as possible after collection. Freezing will hamper recovery of *Clostridium botulinum*, but will not prevent detection of toxin.

- Communication of Results

  - Toxin test results may take up to 4 days to complete after specimens are received. Results will be given by the Placer County Public Health Laboratory. The lack of detection of toxin in serum of patients with clinically compatible illness does not necessarily rule out the diagnosis of botulism, particularly in the event of inhaled botulism neurotoxin.

- Bacterial cultures, antibody tests, and routine laboratory tests

  - Blood, stool, sputum and urine cultures are not helpful in confirming a diagnosis of inhalational botulism.

  - Patients do not generally develop an antibody response due to the subimmunogenic amount of toxin necessary to produce disease.

  - Routine laboratory tests, including chemistries and hematologic profiles are generally within normal limits unless a secondary process (*e.g., nosocomial infection*) has occurred.

  - Cerebrospinal fluid tests are generally normal in botulism (CSF protein may be elevated after 1 – 2 weeks with Guillain Barre Syndrome).

B. Electrophysiologic Studies - Should be performed on clinically-involved muscles

Tensilon test - normal (differentiates botulism from myasthenia gravis)

Nerve conduction velocity - normal

Repetitive nerve stimulation at 50 Hz - facilitation of the compound muscle action potential (rates 20-50 per second)(EMG shows an incremental response to repetitive stimulation)

These studies may support the diagnosis of botulism but a normal electromyelogram does not rule out disease.

V. Handling Laboratory Specimens

Biosafety Level 2 practices, containment equipment and facilities are recommended for all activities with materials known or potentially containing toxin. Laboratory staff handling specimens from persons who might have botulism must wear surgical gloves, protective gowns, and shoe covers if performing procedures with high splash potential or risk of aerosolization. Laboratory tests should be performed in Biological Safety Level 2 cabinets and blood cultures should be maintained in a closed system. Every effort should be made to avoid splashing or creating an aerosol, and protective eye wear and masks should be worn if work cannot be done in a Biological Safety Level 2 cabinet.

Accidental spills of potentially contaminated material should be decontaminated immediately by covering liberally with a disinfectant solution (a strong alkaline solution {e.g, 0.1M sodium hydroxide} for botulinum toxin or a 1:10 bleach solution for the *Clostridium* organism) for at least 15 minutes to ensure effective inactivation. If the material is suspected to contain both toxin and organisms, the spill must be sequentially treated with bleach and sodium hydroxide.

All biohazardous waste should be decontaminated by autoclaving. Contaminated equipment or instruments may be decontaminated with a hypochlorite solution, hydrogen peroxide, peracetic acid, 1% glutaraldehyde solution, formaldehyde, ethylene oxide, copper irradiation, or other O.S.H.A. approved solutions, or by autoclaving or boiling for 10 minutes.

VI. Treatment

Supportive care combined with the *rapid* administration of botulinal antitoxin are the keys to successful management of botulism. With improvements in intensive care support and early administration of antitoxin, mortality rates for botulism have been approximately 6% in recent years. Respiratory failure due to paralysis of respiratory muscles is the most serious complication as well as the most common cause of death.

- Botulinum Antitoxin - In uncontrolled studies, use of antitoxin has been associated with lower mortality rates and, if administered early after onset of symptoms, a shorter course of illness. A licensed trivalent antitoxin is available. Contrary to the package insert directions, current recommendations are to administer ONE 10 ml vial of antitoxin per patient, intravenously in a normal saline solution over 20 minutes. Antitoxin need not be repeated since the circulating antibodies have a half-life of 5 to 8 days. Contact Placer County Health and Human Services Communicable Disease Control (530) 889-7141 (after hours call Health Officer

Richard J. Burton, M.D., M.P.H., at (530) 889-7119) and they will assist in obtaining antitoxin from the state.

- The antitoxin is of equine origin and requires skin testing for hypersensitivity *before* administration of the antitoxin. About 9-21 % of patients will develop either acute or delayed-type sensitivity reactions. Serum sickness reactions appear to be dose-related and may be less likely with the newer dosing recommendations.

  Skin testing is performed by injecting 0.1 ml of a 1:10 dilution (in sterile physiologic saline) of antitoxin intradermally in the patient's forearm with a 26 or 27 gauge needle. The injection site should be monitored and the patient observed for allergic reactions for 20 minutes.

  The skin test is positive if any of the following occur:

  a. Hyperemic areola (> 0.5 cm) at the site of the injection
  b. Fever or chills
  c. Hypotension (greater than 20 mm Hg drop in blood pressure)
  d. Skin rash or generalized itching
  e. Respiratory difficulty
  f. Nausea or vomiting

- Supportive therapy - Improvements in intensive care have significantly decreased mortality rates for botulism. Monitoring of the vital capacity is crucial and intubation is usually indicated when the vital capacity falls below 12ml/kg, without waiting for a rise in PCO2 or fall in oxygen saturation. Ventilatory support may be required for weeks to months.

- Therapy in pediatric patients and pregnant women - therapy is identical to the recommendations outlined above.

- Aminoglycoside antibiotics are contraindicated for treatment of secondary infections since they can exacerbate the neuromuscular blockade.

VII. Isolation of Patients

Botulism has not been transmitted from human-to-human. All staff should observe Standard Precautions when caring for patients with suspected or confirmed botulism. Patients do not require isolation rooms.

VIII. Disposal of Infectious Waste

Use of tracking forms, containment, storage, packaging, treatment and disposal methods should be based upon the same rules as all other regulated medical wastes.

IX. Autopsy and Handling of Corpses

All postmortem procedures are to be performed using Universal Precautions.

- All persons performing or assisting in postmortem procedures must wear mandated P.P.E. (personal protective equipment) as delineated by O.S.H.A. guidelines.
- Instruments should be autoclaved or sterilized with a 10% bleach solution or other solutions approved by O.S.H.A. Surfaces contaminated during postmortem procedures should be decontaminated with an appropriate chemical germicide such as 10% hypochlorite or 5% phenol (carbolic acid).

X. Management of Exposed Persons

An exposed person is defined as a person who has been directly exposed to botulinum neurotoxin. In the case of a bioterrorist event, the exposure will most likely occur by inhalation of toxin.

There is currently no available post-exposure prophylaxis for asymptomatic exposed persons. Such persons should be educated regarding the signs and symptoms of clinical botulism and instructed to seek medical care immediately if symptoms occur.

XI. Reporting

Botulism is a reportable disease in California. *All suspect cases* should be immediately reported by telephone:

- During business hours
  Placer County Health and Human Services, Communicable Disease Control at
  (530) 889-7141
  (In the event that you are unable to reach A Communicable Disease Control

Contact, please call the Placer County Office of Emergency Services at (530) 886-5300)

- After business hours
  Placer County Health Officer, Richard J. Burton, M.D., M.P.H., at **(530) 889-7119**
  (In the event that you are unable to reach A Communicable Disease Control Contact, please call the Placer County Office of Emergency Services 24-hour dispatch at (530) 886-5375)

XII. References

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TULAREMIA

ALL SUSPECT CASES OF TULAREMIA MUST BE REPORTED IMMEDIATELY TO THE HEALTH AND HUMAN SERVICES COMMUNICABLE DISEASE CONTROL:

During business hours: (530) 889-7141
After hours (Health Officer Richard J. Burton, M.D., M.P.H.): (530) 889-7119

***(*In the event that you are unable to reach a Communicable Disease Control Contact, please call the Placer County Office of Emergency Services at (530) 886-5300 during business hours, or 24-hour dispatch at (530) 886-5375 after business hours.)**

Epidemiology:

- Highly infectious after aerosolization
- Infectious dose can be as low as 10-15 organisms
- Person-to-person transmission does not occur

Clinical:

- Incubation period is 3-6 days (ranges 1-21 days)
- Aerosolization would most likely result in typhoidal tularemia, with pneumonic involvement
- Typhoidal tularemia is a nonspecific illness, with fever, headache, malaise and non-productive cough (mortality rates can be as high as 30-60%)
- Diagnosis requires high index of suspicion given nonspecific presentation

Laboratory Diagnosis:

- Bacterial cultures should be handled in a Biosafety Level 3 facility; isolation of organism can otherwise put laboratory workers at risk.
- Organism is difficult to culture and grows poorly on standard media; cysteine-enriched media is required.
- Serology is most commonly used for diagnosis.
- Contact the Placer County Public Health Laboratory for assistance.

Patient Isolation:

- Standard precautions. Respiratory isolation not required.

Treatment:

- Streptomycin (7.5 mg/kg IM q 12 hours x 10-14 days) or gentamicin (3-5 mg/kg/day IV or IM qd in 3 divided doses x 10-14 days) are the preferred antibiotics
- Tetracyclines are alternative choices, although they are bacteriostatic and associated with higher relapse rates and must be continued for at least 14 days

Prophylaxis:

- Antibiotic prophylaxis is most effective if begun within 24 hours after exposure to aerosol
- Tetracyclines are recommended for 14 days

Tularemia as a Biological Weapon
Medical and Public Health Management

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for the Working Group on Civilian Biodefense

Objective The Working Group on Civilian Biodefense has developed consensus-based recommendations for measures to be taken by medical and public health professionals if tularemia is used as a biological weapon against a civilian population.

Participants The working group included 25 representatives from academic medical centers, civilian and military governmental agencies, and other public health and emergency management institutions and agencies.

Evidence MEDLINE databases were searched from January 1966 to October 2000, using the Medical Subject Headings *Francisella tularensis*, *Pasteurella tularensis*, *biological weapon*, *biological terrorism*, *bioterrorism*, *biological warfare*, and *biowarfare*. Review of these references led to identification of relevant materials published prior to 1966. In addition, participants identified other references and sources.

Consensus Process Three formal drafts of the statement that synthesized information obtained in the formal evidence-gathering process were reviewed by members of the working group. Consensus was achieved on the final draft.

Conclusions A weapon using airborne tularemia would likely result 3 to 5 days later in an outbreak of acute, undifferentiated febrile illness with incipient pneumonia, pleuritis, and hilar lymphadenopathy. Specific epidemiological, clinical, and microbiological findings should lead to early suspicion of intentional tularemia in an alert health system; laboratory confirmation of agent could be delayed. Without treatment, the clinical course could progress to respiratory failure, shock, and death. Prompt treatment with streptomycin, gentamicin, doxycycline, or ciprofloxacin is recommended. Prophylactic use of doxycycline or ciprofloxacin may be useful in the early postexposure period.

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I know of no other infection of animals communicable to man that can be acquired from sources so numerous and so diverse. In short, one can but feel that the status of tularemia, both as a disease in nature and of man, is one of potentiality.

R. R. Parker[1]

TULAREMIA, A BACTERIAL ZOONOsis, is the subject of this fifth article in a series providing recommendations for medical and public health management following use of various agents as biological weapons of terrorism.[2-5] The causative agent of tularemia, *Francisella tularensis*, is one of the most infectious pathogenic bacteria known, requiring inoculation or inhalation of as few as 10 organisms to cause disease.[6,7] Humans become incidentally infected through diverse environmental exposures and can develop severe and sometimes fatal illness but do not transmit infection to others. The Working Group on Civilian Biodefense considers *F tularensis* to be a dangerous potential biological weapon because of its extreme infectivity, ease of dissemination, and substantial capacity to cause illness and death.[8-11]

CONSENSUS METHODS

The working group comprised 25 representatives from academic medical centers, civilian and military governmental agencies, and other public health and emergency management institutions. This group followed a specified process in developing a consensus statement. MEDLINE databases from January 1966 to October 2000 were searched

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Ex Officio Participants in the Working Group on Civilian Biodefense are listed at the end of this article.
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using the Medical Subject Headings *Francisella tularensis*, *Pasteurella tularensis*, *biological weapon*, *biological terrorism*, *bioterrorism*, *biological warfare*, and *biowarfare*. Review of the bibliographies of these references led to identification of relevant materials published prior to 1966. In addition, participants identified other published and unpublished references and sources for review.

The first draft of the consensus statement was a synthesis of information obtained in the formal evidence-gathering process. Members of the working group were asked to make written comments on this first draft in May 1999. Subsequent revised drafts were reviewed and edited until full consensus of the working group was achieved.

HISTORY AND POTENTIAL AS A BIOLOGICAL WEAPON

Tularemia was first described as a plague-like disease of rodents in 1911 and, shortly thereafter, was recognized as a potentially severe and fatal illness in humans.[12] Tularemia's epidemic potential became apparent in the 1930s and 1940s, when large waterborne outbreaks occurred in Europe and the Soviet Union[13-15] and epizootic-associated cases occurred in the United States.[16,17] As well, *F tularensis* quickly gained notoriety as a virulent laboratory hazard.[18,19] Public health concerns impelled substantial early investigations into tularemia's ecology, microbiology, pathogenicity, and prevention.[19-22]

Francisella tularensis has long been considered a potential biological weapon. It was one of a number of agents studied at Japanese germ warfare research units operating in Manchuria between 1932 and 1945[23]; it was also examined for military purposes in the West. A former Soviet Union biological weapons scientist, Ken Alibeck, has suggested that tularemia outbreaks affecting tens of thousands of Soviet and German soldiers on the eastern European front during World War II may have been the result of intentional use.[24] Following the war, there were continuing military studies of tularemia. In the 1950s and 1960s, the US military developed weapons that would disseminate *F tularensis* aerosols[10]; concurrently, it conducted research to better understand the pathophysiology of tularemia and to develop vaccines and antibiotic prophylaxis and treatment regimens. In some studies, volunteers were infected with *F tularensis* by direct aerosol delivery systems and by exposures in an aerosol chamber.[10] A live attenuated vaccine was developed that partially protected against respiratory and intracutaneous challenges with the virulent SCHU S-4 strain of *F tularensis*,[6,7] and various regimens of streptomycin, tetracyclines, and chloramphenicol were found to be effective in prophylaxis and treatment.[25-27] By the late 1960s, *F tularensis* was one of several biological weapons stockpiled by the US military.[10] According to Alibeck, a large parallel effort by the Soviet Union continued into the early 1990s and resulted in weapons production of *F tularensis* strains engineered to be resistant to antibiotics and vaccines.[24]

In 1969, a World Health Organization expert committee estimated that an aerosol dispersal of 50 kg of virulent *F tularensis* over a metropolitan area with 5 million inhabitants would result in 250 000 incapacitating casualties, including 19 000 deaths.[28] Illness would be expected to persist for several weeks and disease relapses to occur during the ensuing weeks or months. It was assumed that vaccinated individuals would be only partially protected against an aerosol exposure. Referring to this model, the Centers for Disease Control and Prevention (CDC) recently examined the expected economic impact of bioterrorist attacks and estimated the total base costs to society of an *F tularensis* aerosol attack to be $5.4 billion for every 100 000 persons exposed.[9]

The United States terminated its biological weapons development program by executive order in 1970 and, by 1973, had destroyed its entire biological arsenal.[10] Since then, the US Army Medical Research Institute of Infectious Diseases has been responsible for defensive medical research on *F tularensis* and other potential biological warfare agents to better protect the US military, including protocols on decontamination, prophylaxis, clinical recognition, laboratory diagnosis, and medical management.[29] The CDC operates a national program for bioterrorism preparedness and response that incorporates a broad range of public health partnerships.[30,31]

EPIDEMIOLOGY

Geographic Distribution and Human Exposures

Tularemia occurs throughout much of North America and Eurasia.[15,21,22,32] In the United States, human cases have been reported from every state except Hawaii; however, most cases occur in south-central and western states (especially Missouri, Arkansas, Oklahoma, South Dakota, and Montana).[33-35] In Eurasia, the disease is also widely endemic, although the greatest numbers of human cases are reported from northern and central Europe, especially Scandinavian countries and those of the former Soviet Union.[36,37] Tularemia is almost entirely a rural disease, although urban and suburban exposures occasionally do occur.[38-41]

Throughout its range, *F tularensis* is found in widely diverse animal hosts and habitats and can be recovered from contaminated water, soil, and vegetation.[15,20-22,32] A variety of small mammals, including voles, mice, water rats, squirrels, rabbits, and hares, are natural reservoirs of infection. They acquire infection through bites by ticks, flies, and mosquitoes, and by contact with contaminated environments. Although enzootic cycles of *F tularensis* typically occur without notice, epizootics with sometimes extensive die-offs of animal hosts may herald outbreaks of tularemia in humans.[16,22,42,43] Humans become infected with *F tularensis* by various modes, including bites by infective arthropods,[42,44-47] handling infectious animal tissues or fluids,[17,48,49] direct contact with or ingestion of contaminated water, food, or soil,[13,20,40,50,51] and inhalation of infective aerosols.[43,52-56] Persons of all ages

and both sexes appear to be equally susceptible to tularemia. Certain activities, such as hunting, trapping, butchering, and farming, are most likely to expose adult men. Laboratory workers are especially vulnerable to infection, either by accidentally inoculating themselves or by inhaling aerosolized organisms.[18,22,56-58] Ordinary exposures during examination of an open culture plate can cause infection. Although *F tularensis* is highly infectious and pathogenic, its transmission from person to person has not been documented.

Incidence

The worldwide incidence of tularemia is not known, and the disease is probably greatly underrecognized and underreported. In the United States, reported cases have dropped sharply from several thousand per year prior to 1950 to less than 200 per year in the 1990s.[33-35] Between 1985 and 1992, 1409 cases and 20 deaths were reported in the United States, for a mean of 171 cases per year and a case-fatality rate of 1.4%.[34] Persons in all age groups were affected, but most were children younger than 10 years and adults aged 50 years or older. Of 1298 cases for which information on sex was available, 942 (72.6%) occurred in males, and males outnumbered females in all age groups. Most cases occur in June through September, when arthropod-borne transmission is most common.[17,35,59] Cases in winter usually occur among hunters and trappers who handle infected animal carcasses.[17,35,48] In the United States, cases are mostly sporadic or occur in small clusters[34,35,49]; in Eurasia, waterborne, arthropod-borne, and airborne outbreaks involving hundreds of persons have been reported.[40,43,44,51,53-55]

Natural Occurrences of Inhalational Tularemia

The largest recorded airborne tularemia outbreak occurred in 1966-1967 in an extensive farming area of Sweden.[43] This outbreak involved more than 600 patients infected with strains of the milder European biovar of *F tularensis* (*F tularensis* biovar palaearctica) [type B]), most of whom acquired infection while doing farm work that created contaminated aerosols. Case exposures and disease onsets occurred during a period of months but peaked during the winter, when rodent-infested hay was being sorted and moved from field storage sites to barns. Among 140 serologically confirmed cases thought to have been infected by inhalation, most had typical acute symptoms of fever, fatigue, chills, headache, and malaise; only 14 (10%) of confirmed patients had symptoms of pneumonia, such as dyspnea and chest pains. Patients generally responded well to tetracycline, and no deaths were reported. Inhalational tularemia in the United States has involved only single cases or small clusters of cases, variously resulting from laboratory exposures,[18,56,57] disturbance of contaminated animal carcasses,[38,39,41] and suspected infective environmental aerosols.[41,52] Cases of inhalational tularemia in the United States are thought to be due mostly to the more virulent *F tularensis* biovar tularensis (type A) and usually follow an acute and severe course, with prominent pneumonitis. Some cases, however, have radiographic evidence of pleuropneumonia with minimal or absent respiratory signs on physical examination.[39,41,52]

Although airborne *F tularensis* would be expected to principally cause primary pleuropneumonic infection, some exposures might contaminate the eye, resulting in ocular tularemia; penetrate broken skin, resulting in ulceroglandular or glandular disease; or cause oropharyngeal disease with cervical lymphadenitis. In the aforementioned Swedish outbreak, conjunctivitis was reported in 26% of 140 confirmed cases and an infected ulcer of the skin was reported in nearly 12%; pharyngitis was reported in 31% and oral ulcers in about 9% of the cases; and 32% of these patients had various exanthemas, such as erythema multiforme and erythema nodosum.[43] Tularemia outbreaks arising from similar agricultural exposures have been reported from Finland,[53] mostly presenting with general constitutional symptoms rather than specific manifestations of pneumonia; enlargement of hilar nodes was the principal radiographic finding in these cases.[54]

Inhalational Tularemia Following Use as a Biological Weapon

Although *F tularensis* could be used as a weapon in a number of ways, the working group believes that an aerosol release would have the greatest adverse medical and public health consequences. Release in a densely populated area would be expected to result in an abrupt onset of large numbers of cases of acute, nonspecific febrile illness beginning 3 to 5 days later (incubation range, 1-14 days), with pleuropneumonitis developing in a significant proportion of cases during the ensuing days and weeks. Public health authorities would most likely become aware of an outbreak of unusual respiratory disease in its early stages, but this could be difficult to distinguish from a natural outbreak of community-acquired infection, especially influenza or various atypical pneumonias. The abrupt onset of large numbers of acutely ill persons, the rapid progression in a relatively high proportion of cases from upper respiratory symptoms and bronchitis to life-threatening pleuropneumonitis and systemic infection affecting, among others, young, previously healthy adults and children should, however, quickly alert medical professionals and public health authorities to a critical and unexpected public health event and to bioterrorism as a possible cause (TABLE 1). Until the etiology became clear, clinicians would need to work closely with epidemiologists and diagnostic laboratories to differentiate the illness from various community-acquired pneumonias and to determine if it could have resulted from use of one of several potential bioterrorism weapons agents, such as those causing tularemia, plague, anthrax, or Q fever.[2,4,29]

In general, tularemia would be expected to have a slower progression of illness and a lower case-fatality rate than either inhalational plague or anthrax. Plague would most likely progress very

Table 1. Diagnosis of Inhalational Tularemia Following Use of a Biological Weapon

Clinical Findings
Sudden onset of acute febrile illness, progressing in some patients to pharyngitis, bronchiolitis, pneumonitis, pleuritis, hilar lymphadenitis. Complications of overwhelming untreated infection may lead to sepsis and inflammatory response syndrome.
Epidemiology
Point-source outbreak pattern; likely urban, nonagricultural setting. Unexpected severe respiratory illness in otherwise healthy persons. Risk related to degree of exposure with no differences in susceptibility by age or sex.
Microbiology
Small, gram-negative coccobacilli in direct stain of respiratory secretions. Sputum, tracheobronchial secretions, and blood should be cultured using cysteine-enriched medium. Antimicrobial susceptibility of isolates should be determined. Direct fluorescent antibody stain is first-line, rapid identification procedure at reference laboratories. Polymerase chain reaction and antigen detection procedures may also provide rapid identification. Microagglutination assay can detect serum antibodies beginning 10 days after illness onset. Virulence testing and molecular genetic characterizations are performed at specialized laboratories.
Pathology
Histological findings of acute suppurative necrosis followed by granulomatous reactions. Target organs include lungs, lymph nodes, spleen, liver, and kidney.
Radiology
Peribronchial infiltrates leading to bronchopneumonia in 1 or more lobes, often accompanied by pleural effusion and enlarged hilar nodes. Signs may be absent or minimal, with only 1 or several small, discrete pulmonary infiltrates, or scattered granulomatous lesions of lung parenchyma or pleura.

rapidly to severe pneumonia, with copious watery or purulent sputum production, hemoptysis, respiratory insufficiency, sepsis, and shock.[4] Inhalational anthrax would be differentiated by its characteristic radiological findings of prominent symmetric mediastinal widening and absence of bronchopneumonia.[2] As well, anthrax patients would be expected to develop fulminating, toxic, and fatal illness despite antibiotic treatment.[29] Milder forms of inhalational tularemia could be clinically indistinguishable from Q fever; establishing a diagnosis of either would be problematic without reference laboratory testing. Presumptive laboratory diagnoses of plague or anthrax would be expected to be made relatively quickly, although microbiological confirmation could take days. Isolation and identification of *F tularensis* using routine laboratory procedures could take several weeks.

Once a substantial cluster of cases of inhalational tularemia had been identified, epidemiological findings should suggest a bioterrorist event. The abrupt onset and single peak of cases would implicate a point-source exposure without secondary transmission. Among exposed persons, attack rates would likely be similar across sex and age groups, and risk would be related to degree of exposure to the point source (Table 1). An outbreak of inhalational tularemia in an urban setting should trigger a high level of suspicion of an intentional event, since all reported inhalational tularemia outbreaks have occurred in rural areas.

MICROBIOLOGY AND VIRULENCE FACTORS

Francisella tularensis is a small, nonmotile, aerobic, gram-negative coccobacillus. It has a thin lipopolysaccharide-containing envelope and is a hardy non–spore-forming organism that survives for weeks at low temperatures in water, moist soil, hay, straw, and decaying animal carcasses.[21,22,60,61] *Francisella tularensis* has been divided into 2 major subspecies (biovars) by virulence testing, biochemical reactions, and epidemiological features.[62] *Francisella tularensis* biovar tularensis (type A) may be highly virulent in humans and animals, produces acid from glycerol, demonstrates citrulline ureidase activity, and is the most common biovar isolated in North America.[22,60] *Francisella tularensis* biovar palaearctica (type B) is relatively avirulent, does not produce acid from glycerol, and does not demonstrate citrulline ureidase activity. In Europe and Asia, all human tularemia is thought to be caused by the milder type B strains, although recent studies there have identified naturally occurring *F tularensis* related to *F tularensis* biovar tularensis.[63,64] A few rapidly growing strains of *F tularensis* have been recovered from the blood of immunocompromised patients not showing seroreactivity to *F tularensis*.[65]

Transformed plasmids have been engineered to express chloramphenicol and tetracycline resistance in *F tularensis*.[66] Virulent, streptomycin-resistant *F tularensis* strains have been examined in biowarfare agent studies both in the United States and the Soviet Union.[24,27,56] Although *F tularensis* virulence factors are poorly understood and characterized,[67,68] it is possible that strain virulence could be enhanced through laboratory manipulation.

PATHOGENESIS AND CLINICAL MANIFESTATIONS

Pathogenesis

Francisella tularensis can infect humans through the skin, mucous membranes, gastrointestinal tract, and lungs. It is a facultative intracellular bacterium that multiplies within macrophages.[68,69] The major target organs are the lymph nodes, lungs and pleura, spleen, liver, and kidney.[19,20,49,70-72] Untreated, bacilli inoculated into skin or mucous membranes multiply, spread to the regional lymph nodes and further multiply, and may then disseminate to organs throughout the body. Bacteremia may be common in the early phase of infection. The initial tissue reaction to infection is a focal, intensely suppurative necrosis consisting largely of accumulations of polymorphonuclear leukocytes, followed by invasion of macrophages, epithelioid cells, and lymphocytes. Suppurative lesions become granulomatous, and histopathological examination of the granulomas shows a central necrotic, sometimes caseating zone surrounded by a layer of epithelioid cells, multinucleated giant cells, and fibroblasts in a radial arrange-

ment, typical of other granulomatous conditions, such as tuberculosis and sarcoidosis.[20,70,71]

Monkeys that inhaled the virulent SCHU S-4 strain of *F tularensis* (type A) developed acute bronchiolitis within 24 hours of exposure to 1-µm particles and within 48 hours of exposure to 8-µm particles.[73] By 72 hours following challenge, inflammation was present in peribronchial tissues and alveolar septa. Bronchopneumonia was most pronounced in animals exposed to the smaller particles and was characterized by tracheobronchial lymph node enlargement and reddish, firm, 0.2- to 0.5-cm-diameter discrete inflammatory lesions scattered throughout the lungs. In the absence of treatment, the disease progressed to pneumonic consolidation and organization, granuloma formation, and eventual chronic interstitial fibrosis.

Humans with inhalational exposures also develop hemorrhagic inflammation of the airways early in the course of illness, which may progress to bronchopneumonia.[54] Histopathological examination of affected lungs shows alveolar spaces filled with an exudate of mononuclear cells. Pleuritis with adhesions and effusion and hilar lymphadenopathy are common radiological and pathological findings.[70,72]

Clinical Manifestations

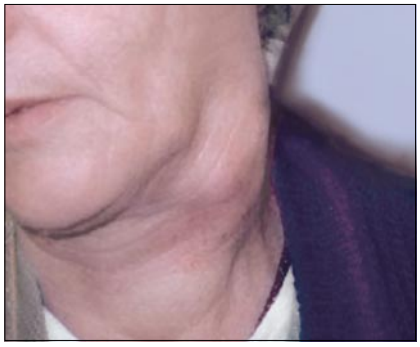
The primary clinical forms of tularemia vary in severity and presentation according to virulence of the infecting organism, dose, and site of inoculum. Primary disease presentations include ulceroglandular, glandular, oculoglandular, oropharyngeal, pneumonic, typhoidal, and septic forms.[19,20,49,70,72,74,75] The term *typhoidal tularemia* has been used to describe illness in tularemia patients with systemic infections manifesting as fever and other constitutional signs without cutaneous or mucosal membrane lesions or regional lymphadenitis. Sometimes, these patients present with prominent gastrointestinal manifestations, such as diarrhea and pain. Confusion is created when *typhoidal tularemia* is used to describe the illness in patients infected by inhalation, especially when there are signs of pleuropneumonic disease; this usage can be misleading and has been discouraged.[54,75]

The onset of tularemia is usually abrupt, with fever (38°C-40°C), headache, chills and rigors, generalized body aches (often prominent in the low back), coryza, and sore throat. A pulse-temperature dissociation has been noted in as many as 42% of patients.[49] A dry or slightly productive cough and substernal pain or tightness frequently occur with or without objective signs of pneumonia, such as purulent sputum, dyspnea, tachypnea, pleuritic pain, or hemoptysis.[7,19,26,70,74] Nausea, vomiting, and diarrhea sometimes occur. Sweats, fever and chills, progressive weakness, malaise, anorexia, and weight loss characterize the continuing illness. Studies of volunteers have shown that *F tularensis* aerosol exposures can incapacitate some persons in the first 1 or 2 days of illness, and significant impairment in performing tasks can continue for days after antibiotic treatment is begun.[76] In untreated tularemia, symptoms often persist for several weeks and, sometimes, for months, usually with progressive debility. Any form of tularemia may be complicated by hematogenous spread, resulting in secondary pleuropneumonia, sepsis, and, rarely, meningitis.[74,77]

Prior to the advent of antibiotics, the overall mortality from infections with the more severe type A strains was in the range of 5% to 15%, and fatality rates as high as 30% to 60% were reported for untreated pneumonic and severe systemic forms of disease.[72,78] Currently, the overall case-fatality rate of reported cases in the United States is less than 2%.[34,49] Type B infections are rarely fatal.

In ulceroglandular tularemia, the form that typically arises from handling a contaminated carcass or following an infective arthropod bite, a local cutaneous papule appears at the inoculation site at about the time of onset of generalized symptoms, becomes pustular, and ulcerates within a few days of its first appearance. The ulcer is tender, generally has an indolent character, and may be covered by an eschar. Typically, one or more regional afferent lymph nodes may become enlarged and tender within several days of the appearance of the papule. Even with antibiotic treatment, the affected nodes may become fluctuant and rupture. In oculoglandular tularemia, which follows direct contamination of the eye, ulceration occurs on the conjunctiva, accompanied by pronounced chemosis, vasculitis, and regional lymphadenitis. Glandular tularemia is characterized by lymphadenopathy without an ulcer.

Figure 1. Cervical Lymphadenitis in a Patient With Pharyngeal Tularemia

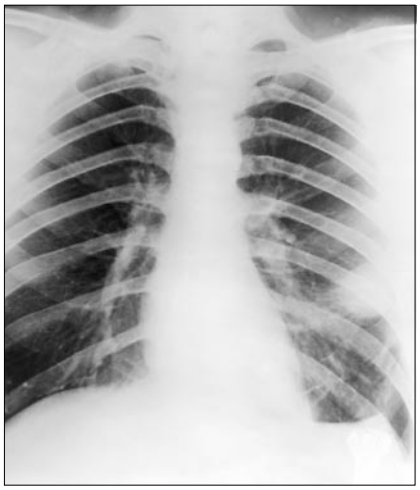


Patient has marked swelling and fluctuant suppuration of several anterior cervical nodes. Infection was acquired by ingestion of contaminated food or water. Source: World Health Organization.

Oropharyngeal tularemia is acquired by drinking contaminated water, ingesting contaminated food, and, sometimes, by inhaling contaminated droplets or aerosols.[14,20,36,43,50,51,79] Affected persons may develop stomatitis but more commonly develop exudative pharyngitis or tonsillitis, sometimes with ulceration. Pronounced cervical or retropharyngeal lymphadenopathy may occur (FIGURE 1).[74,79]

Tularemia pneumonia can be the direct result of inhaling contaminated aerosols or be secondary to hematogenous spread from a distal site. An aerosol release of *F tularensis* would be expected to result in acute illness with signs and symptoms of 1 or more of pharyngitis, bronchiolitis, pleuropneumonitis, and hilar lymphadenitis, accompanied by various manifesta-

Figure 2. Chest Radiograph of a Patient With Pulmonary Tularemia



Infiltrates in left lower lung, tenting of diaphragm, probably caused by pleural effusion, and enlargement of left hilum. Source: Armed Forces Institute of Pathology.

Box. Clinicians Caring for Patients With Suspected Tularemia Should Immediately Contact Their:

(1) Hospital epidemiologist or infection control practitioner and

(2) Local or state health departments

Consult your local telephone operator, the telephone directory under "governmental listings," or the Internet at http://www.cdc.gov/other.htm#states or http://www.astho.org/state.html

If the local and state health departments are unavailable, contact the Centers for Disease Control and Prevention at (970) 221-6400 or http://www.cdc.gov/ncidod/dvbid/dvbid.htm

tions of systemic illness. Inhalational exposures, however, commonly result in an initial clinical picture of systemic illness without prominent signs of respiratory disease.[7,43,53,56] The earliest pulmonary radiographic findings of inhalational tularemia may be peribronchial infiltrates, typically advancing to bronchopneumonia in 1 or more lobes, and often accompanied by pleural effusions and hilar lymphadenopathy (FIGURE 2).[72,75] Signs may, however, be minimal or absent, and some patients will show only 1 or several small, discrete pulmonary infiltrates or scattered granulomatous lesions of lung parenchyma or pleura. Although volunteers challenged with aerosols of virulent *F tularensis* (type A) regularly developed systemic symptoms of acute illness 3 to 5 days following exposure, only 25% to 50% of participants had radiological evidence of pneumonia in the early stages of infection.[7,26] On the other hand, pulmonary infection can sometimes rapidly progress to severe pneumonia, respiratory failure, and death.[72,80] Lung abscesses occur infrequently.[75]

Typhoidal tularemia is used to describe systemic illness in the absence of signs indicating either site of inoculation or anatomic localization of infection. This should be differentiated from inhalational tularemia with pleuropneumonic disease.[54,75]

Tularemia sepsis is potentially severe and fatal. As in typhoidal tularemia, nonspecific findings of fever, abdominal pain, diarrhea, and vomiting may be prominent early in the course of illness. The patient typically appears toxic and may develop confusion and coma. Unless treated promptly, septic shock and other complications of systemic inflammatory response syndrome may ensue, including disseminated intravascular coagulation and bleeding, acute respiratory distress syndrome, and organ failure.[80]

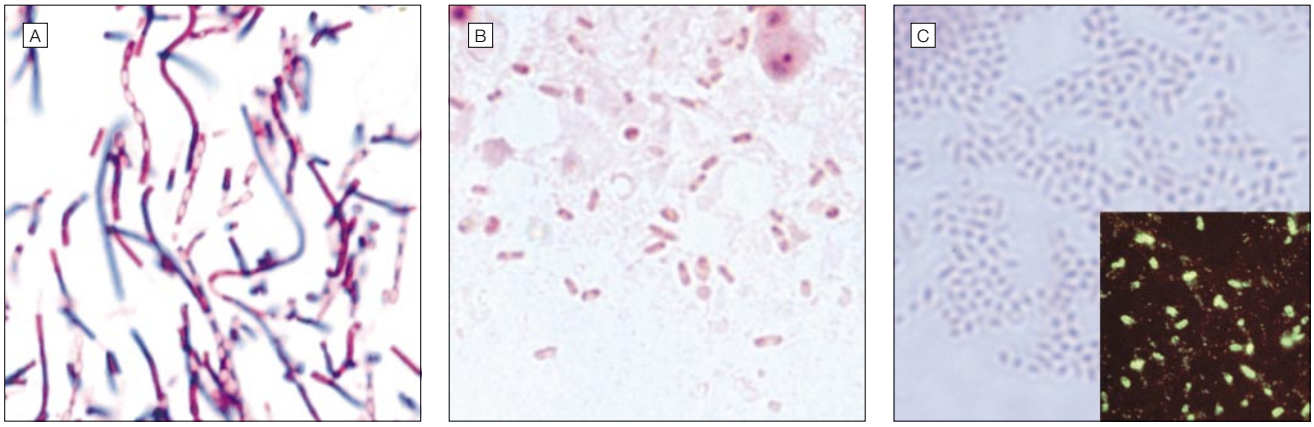
DIAGNOSIS

Tularemia in humans occurs infrequently, resulting in a low index of diagnostic suspicion among clinicians and laboratorians. Since rapid diagnostic testing for tularemia is not widely available, the first indication of intentional tularemia might follow recognition by public health authorities of a clustering of acute, severe respiratory illness with unusual epidemiological features (Table 1). Suspicion of tularemia might be triggered in alert clinicians encountering patients with findings of atypical pneumonia, pleuritis, and hilar lymphadenopathy. Identification of *F tularensis* in clinical specimens may be missed or delayed for days or weeks when procedures for routine microbiological screening of bacterial pathogens are followed, and it is unlikely that a serendipitous laboratory identification would be the sentinel event that alerted authorities to a major bioterrorism action.

Physicians who suspect inhalational tularemia should promptly collect specimens of respiratory secretions and blood and alert the laboratory to the need for special diagnostic and safety procedures. *Francisella tularensis* may be identified by direct examination of secretions, exudates, or biopsy specimens using direct fluorescent antibody or immunohistochemical stains.[81-83] By light microscopy, the organism is characterized by its small size (0.2 μm × 0.2-0.7 μm), pleomorphism, and faint staining. It does not show the bipolar staining characteristics of *Yersinia pestis*,[4] the agent of plague, and is easily distinguished from the large gram-positive rods characteristic of vegetative forms of *Bacillus anthracis* (FIGURE 3).[2] Microscopic demonstration of *F tularensis* using fluorescent-labeled antibodies is a rapid diagnostic procedure performed in designated reference laboratories in the National Public Health Laboratory Network; test results can be made available within several hours of receiving the appropriate specimens if the laboratory is alerted and prepared. Suspicion of inhalational tularemia must be promptly reported to local or state public health authorities so timely epidemiological and environmental investigations can be made (BOX).

Growth of *F tularensis* in culture is the definitive means of confirming the diagnosis of tularemia.[60,81] *Francisella tularensis* can be grown from pharyngeal washings, sputum specimens, and even fasting gastric aspirates in a high proportion of patients with inhalational tularemia.[56] It is only occasionally isolated from the blood. *Fran-*

Figure 3. Gram Stain Smears of the Agents of Anthrax (*Bacillus anthracis*), Plague (*Yersinia pestis*), and Tularemia (*Francisella tularensis*), Demonstrating Comparative Morphology, Size, and Staining Characteristics

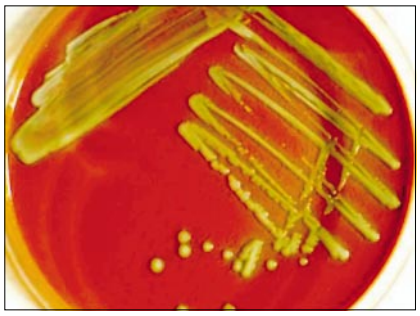


A, *B anthracis* is a large (0.5-1.2 µm × 2.5-10.0 µm), chain-forming, gram-positive rod that sporulates under certain conditions (Gram stain of organism from culture; original magnification ×250); B, *Y pestis* is a gram-negative, plump, non–spore-forming, bipolar-staining bacillus that is approximately 0.5-0.8 µm × 1-3 µm (Gram stain of smear from infected tissue; original magnification ×250); C, *F tularensis* is a small (0.2 µm × 0.2-0.7 µm), pleomorphic, poorly staining, gram-negative coccobacillus (Gram stain of organism from culture; original magnification ×500) (inset, direct immunofluorescence of smear of *F tularensis*; original magnification ×400. Sources: A and B, Sherif Zaki, Centers for Disease Control and Prevention; C, Armed Forces Institute of Pathology.

cisella tularensis grows best in cysteine-enriched broth and thioglycollate broth and on cysteine heart blood agar, buffered charcoal-yeast agar, and chocolate agar. Selective agar (such as chocolate agar selective for *Neisseria gonorrhea* isolation) may be useful when culturing materials from nonsterile sites, such as sputum. Inoculated media should be incubated at 37°C. Although growth may be visible as early as 24 to 48 hours after inoculation, growth may be delayed and cultures should be held for at least 10 days before discarding. Under ideal conditions, bacterial colonies on cysteine-enriched agar are typically 1 mm in diameter after 24 to 48 hours of incubation and 3 to 5 mm in diameter by 96 hours.[60,81] On cysteine heart agar, *F tularensis* colonies are characteristically opalescent and do not discolor the medium (FIGURE 4).

Antigen detection assays, polymerase chain reaction, enzyme-linked immunoassays, immunoblotting, pulsed-field gel electrophoresis, and other specialized techniques may be used to identify *F tularensis* and to characterize strains.[84-87] These procedures are usually performed only in research and reference laboratories, however. In laboratories where advanced methods are established, results of antigen detection and polymerase chain reaction analyses can be obtained within several hours of receipt of isolates. Typically, serum antibody titers do not attain diagnostic levels until 10 or more days after onset of illness, and serology would provide minimal useful information for managing an outbreak. Serological confirmation of cases, however, may be of value for forensic or epidemiological purposes. Most laboratories use tube agglutination or microagglutination tests that detect combined immunoglobulin M and immunoglobulin G.[84,85] A 4-fold change in titer between acute and convalescent serum specimens, a single titer of at least 1:160 for tube agglutination or 1:128 for microagglutination is diagnostic for *F tularensis* infection. Information on reference diagnostic testing and shipping/handling of specimens can be obtained from state public health laboratories and from the Division of Vector-Borne Infectious Diseases, CDC, Fort Collins, Colo (telephone: [970] 221-6400; e-mail: dvbid@cdc.gov).

Figure 4. *Francisella tularensis* Growth at 72 Hours After Inoculation



These *Francisella tularensis* colonies show characteristic opalescence on cysteine heart agar with sheep blood (cultured at 37°C for 72 hours). Source: Centers for Disease Control and Prevention.

VACCINATION

Beginning in the 1930s, the Soviet Union used a live attenuated vaccine to immunize tens of millions of persons living in tularemia-endemic areas.[88] In the United States, a live attenuated vaccine derived from the avirulent live vaccine strain has been used to protect laboratorians routinely working with *F tularensis*; until recently, this vaccine was available as an investigational new drug.[89] It is currently under review by the US Food and Drug Administration (FDA), and its future availability is undetermined.

In a retrospective study of civilians working with *F tularensis* at a US Army research facility, the incidence of accidental acute inhalational tularemia among laboratorians declined from 5.70 cases per 1000 person-years of risk at

Table 2. Working Group Consensus Recommendations for Treatment of Patients With Tularemia in a Contained Casualty Setting*

Contained Casualty Recommended Therapy
Adults
Preferred choices
Streptomycin, 1 g IM twice daily
Gentamicin, 5 mg/kg IM or IV once daily†
Alternative choices
Doxycycline, 100 mg IV twice daily
Chloramphenicol, 15 mg/kg IV 4 times daily†
Ciprofloxacin, 400 mg IV twice daily†
Children
Preferred choices
Streptomycin, 15 mg/kg IM twice daily (should not exceed 2 g/d)
Gentamicin, 2.5 mg/kg IM or IV 3 times daily†
Alternative choices
Doxycycline; if weight ≥45 kg, 100 mg IV twice daily; if weight <45 kg, give 2.2 mg/kg IV twice daily
Chloramphenicol, 15 mg/kg IV 4 times daily†
Ciprofloxacin, 15 mg/kg IV twice daily†‡
Pregnant Women
Preferred choices
Gentamicin, 5 mg/kg IM or IV once daily†
Streptomycin, 1 g IM twice daily
Alternative choices
Doxycycline, 100 mg IV twice daily
Ciprofloxacin, 400 mg IV twice daily†

*Treatment with streptomycin, gentamicin, or ciprofloxacin should be continued for 10 days; treatment with doxycycline or chloramphenicol should be continued for 14-21 days. Persons beginning treatment with intramuscular (IM) or intravenous (IV) doxycycline, ciprofloxacin, or chloramphenicol can switch to oral antibiotic administration when clinically indicated.
†Not a US Food and Drug Administration–approved use.
‡Ciprofloxacin dosage should not exceed 1 g/d in children.

Table 3. Working Group Consensus Recommendations for Treatment of Patients With Tularemia in a Mass Casualty Setting and for Postexposure Prophylaxis*

Mass Casualty Recommended Therapy
Adults
Preferred choices
Doxycycline, 100 mg orally twice daily
Ciprofloxacin, 500 mg orally twice daily†
Children
Preferred choices
Doxycycline; if ≥45 kg, give 100 mg orally twice daily; if <45 kg, give 2.2 mg/kg orally twice daily
Ciprofloxacin, 15 mg/kg orally twice daily†‡
Pregnant Women
Preferred choices
Ciprofloxacin, 500 mg orally twice daily†
Doxycycline, 100 mg orally twice daily

*One antibiotic, appropriate for patient age, should be chosen from among alternatives. The duration of all recommended therapies in Table 3 is 14 days.
†Not a US Food and Drug Administration–approved use.
‡Ciprofloxacin dosage should not exceed 1 g/d in children.

a time when a killed vaccine was in use to 0.27 cases per 1000 person-years of risk after introduction of the live vaccine.[58] Although the incidence of ulceroglandular disease remained unchanged in the 2 periods, signs and symptoms were considered milder among those who received the live vaccine. In volunteer studies, the live attenuated vaccine did not protect all recipients against aerosol challenges with virulent *F tularensis*.[7,26]

Correlates of protective immunity appear about 2 weeks following natural infection or vaccination. Given the short incubation period of tularemia and incomplete protection of current vaccines against inhalational tularemia, vaccination is not recommended for postexposure prophylaxis. The working group recommends use of the live vaccine strain only for laboratory personnel routinely working with *F tularensis*.

TREATMENT

Contained Casualty Situation

Adults. In a contained casualty situation, in which logistics permit individual medical management, the working group recommends parenteral antimicrobial therapy for tularemia (TABLE 2). Streptomycin is the drug of choice.[49,74,90,91] Gentamicin, which is more widely available and may be used intravenously, is an acceptable alternative.[49,74,90-93] Treatment with aminoglycosides should be continued for 10 days. Tetracyclines and chloramphenicol are also used to treat tularemia[49,74,90]; however, relapses and primary treatment failures occur at a higher rate with these bacteriostatic agents than with aminoglycosides, and they should be given for at least 14 days to reduce chance of relapse.[27,74,90] Fluoroquinolones, which have intracellular activity, are promising candidates for treating tularemia. Ciprofloxacin, which is not labeled for use in tularemia, has been shown to be active against *F tularensis* in vitro[94] and in animals[95] and has been used to successfully treat tularemia in both adults and children.[90,94,96,97] Treatment with ciprofloxacin should be continued for 10 days. In persons beginning treatment with parenteral doxycycline, ciprofloxacin, or chloramphenicol, therapy can be switched to oral antibiotic administration when clinically indicated. Very limited experiences in treating tularemia patients with β-lactam and macrolide antibiotics have been reported, and treatment failures have occurred.[98] Use of β-lactam and macrolide antibiotics in treating tularemia is neither FDA-approved nor recommended by the working group.

Children. In children, streptomycin or gentamicin is recommended by the working group as first-line treatment in a contained casualty situation (Table 2). Doxycycline, ciprofloxacin (≤1 g/d), and chloramphenicol can be used as alternatives to aminoglycosides. Fluoroquinolones have been reported to cause cartilage damage in immature animals and are not FDA-approved for use in children. However, short courses of these agents have not been associated with arthropathy in pediatric patients, and the potential risks of their use must be weighed against their benefits in treating serious infections.[96,99,100]

Mass Casualty Situation

Doxycycline and ciprofloxacin, administered orally, are the preferred choices for treatment in the mass casualty setting, for both adults and children (TABLE 3). The ciprofloxacin dosage for children should not exceed 1 g/d. In a mass casualty situation, the working group believes the benefits to children from short courses of doxycycline or fluoroquinolones (Table 3) outweigh the risks of their use.

Since it is unknown whether drug-resistant organisms might be used in a bioterrorist event, antimicrobial susceptibility testing of isolates should be conducted quickly and treatments altered according to test results and clinical responses.

Antibiotics for treating patients infected with tularemia in a bioterrorism scenario are included in a national pharmaceutical stockpile

maintained by the CDC, as are ventilators and other emergency equipment needed to respond to situations of large numbers of critically ill persons that strip local and state resources.[30]

Management of Special Groups

Pregnant Women. In a contained casualty situation, short courses of gentamicin are likely to pose a low risk to fetuses when used to treat tularemia in pregnant women (Table 2). Rare cases of fetal nerve deafness and renal damage have been reported with other aminoglycosides but have not been reported with gentamicin. The benefits of gentamicin in treating pregnant women with tularemia are expected to outweigh any potential risk to fetuses. In a mass casualty situation, oral ciprofloxacin is considered the best alternative to gentamicin for pregnant women (Table 3).

Immunosuppressed Persons. There is scant experience in treating tularemia in immunocompromised patients. However, considering the greater occurrence in immunocompetent patients of tularemia relapses and treatment failures following use of bacteriostatic antimicrobial agents compared with aminoglycosides, streptomycin or gentamicin should be used when possible to treat patients with known immune dysfunction in either contained casualty or mass casualty situations (Table 2).

POSTEXPOSURE ANTIBIOTIC RECOMMENDATIONS

Persons beginning treatment with streptomycin, gentamicin, doxycycline, or ciprofloxacin in the incubation period of tularemia and continuing treatment daily for 14 days might be protected against symptomatic infection. In studies of aerosol challenge with infective doses of the virulent SCHU S-4 strain of *F tularensis*, each of 8 volunteers given oral dosages of tetracycline, 1 g/d for 28 days, and each of 8 volunteers given tetracycline, 2 g/d for 14 days, were fully protected when treatment was begun 24 hours following challenge.[27] Two of 10 volunteers given tetracycline, 1 g/d for only 5 days, developed symptomatic tularemia after antibiotic treatment was stopped.

In the unlikely event that authorities quickly become aware that an *F tularensis* biological weapon has been used and are able to identify and reach exposed persons during the early incubation period, the working group recommends that exposed persons be prophylactically treated with 14 days of oral doxycycline or ciprofloxacin (Table 3). In a circumstance in which the weapon attack has been covert and the event is discovered only after persons start to become ill, persons potentially exposed should be instructed to begin a fever watch. Persons who develop an otherwise unexplained fever or flulike illness within 14 days of presumed exposure should begin treatment as outlined in Tables 2 and 3.

In the laboratory, persons who have had potentially infective exposures to *F tularensis* should be administered oral postexposure antibiotic prophylaxis if the risk of infection is high (eg, spill, centrifuge accident, or needlestick). If the risk is low, exposed persons can be placed on a fever watch and treated if they develop symptoms.

Postexposure prophylactic antibiotic treatment of close contacts of tularemia patients is not recommended since human-to-human transmission of *F tularensis* is not known to occur.

INFECTION CONTROL

Isolation is not recommended for tularemia patients, given the lack of human-to-human transmission. In hospitals, standard precautions[101] are recommended by the working group for treatment of patients with tularemia.

Microbiology laboratory personnel should be alerted when tularemia is clinically suspected. Routine diagnostic procedures can be performed in biological safety level 2 (BSL-2) conditions. Examination of cultures in which *F tularensis* is suspected should be carried out in a biological safety cabinet. Manipulation of cultures and other activities involving infectious materials with a potential for aerosol or droplet production (centrifuging, grinding, vigorous shaking, growing cultures in volume, animal studies) require BSL-3 conditions.[102] When *F tularensis* is presumptively identified in a routine BSL-2 clinical laboratory (level A), specimens should be forwarded to a BSL-3 laboratory (level B) (eg, a state public health laboratory) for confirmation of agent and other studies, such as antimicrobial susceptibility testing.[11] Bodies of patients who die of tularemia should be handled using standard precautions. Autopsy procedures likely to cause aerosols, such as bone sawing, should be avoided. Clothing or linens contaminated with body fluids of patients infected with *F tularensis* should be disinfected per standard precautions protocols.[101]

ENVIRONMENTAL DECONTAMINATION AND PROTECTION

Under natural conditions, *F tularensis* may survive for extended periods in a cold, moist environment. The working group lacks information on survival of intentionally dispersed particles but would expect a short half-life due to desiccation, solar radiation, oxidation and other environmental factors, and a very limited risk from secondary dispersal. In circumstances of a laboratory spill or intentional use in which authorities are concerned about an environmental risk (eg, inanimate surfaces wet with material thought to contain *F tularensis*), decontamination can be achieved by spraying the suspected contaminant with a 10% bleach solution (1 part household bleach and 9 parts water). After 10 minutes, a 70% solution of alcohol can be used to further clean the area and reduce the corrosive action of the bleach. Soap water can be used to flush away less hazardous contaminations. Persons with direct exposure to powder or liquid aerosols containing *F tularensis* should wash body surfaces and clothing with soap water. Standard levels of chlorine in municipal water sources should protect against waterborne infection.[60] Following an urban release, the risk to humans of acquiring tula-

remia from infected animals or arthropod bites is considered minimal and could be reduced by educating the public on simple avoidance of sick or dead animals and on personal protective measures against biting arthropods.

ADDITIONAL RESEARCH

Simple, rapid, and reliable diagnostic tests that could be used to identify persons infected with *F tularensis* in the mass exposure setting need to be developed. Further methods should be designed to rapidly define the molecular genetic characteristics of organisms, especially as they may relate to engineered attributes, such as enhanced virulence and resistance to antimicrobial agents or normally lethal environmental conditions. Complete sequencing and analysis of the genome of natural strains of *F tularensis* would provide an archival base for understanding genetic variants, functions of genes, and mechanisms of action useful in developing means to protect against *F tularensis*. Research is also needed to develop accurate and reliable procedures to rapidly detect *F tularensis* in environmental samples.

New technologies should be explored for developing active (eg, DNA-based) or passive (eg, monoclonal antibody–based) vaccines for rapid preexposure or postexposure protection.

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Disclaimers: In some instances, the indications, dosages, and other information in this article are not consistent with current approved labeling by the US Food and Drug Administration (FDA). The recommendations on use of drugs and vaccine for uses not approved by the FDA do not represent the official views of the FDA nor of any of the federal agencies whose scientists participated in these discussions. Unlabeled uses of the products recommended are noted in the sections of this article in which these products are discussed. Where unlabeled uses are indicated, information used as the basis for the recommendation is discussed.

The views, opinions, assertions, and findings contained herein are those of the authors and should not be construed as official US Department of Defense or US Department of Army positions, policies, or decisions unless so designated by other documentation.

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PLACER COUNTY
HEALTH AND HUMAN SERVICES
COMMUNICABLE DISEASE CONTROL

Medical Treatment and Response to Suspected Tularemia: Information for Health Care Providers During Biologic Emergencies

ALL SUSPECT CASES OF TULAREMIA MUST BE REPORTED IMMEDIATELY TO THE PLACER COUNTY HEALTH AND HUMAN SERVICES, COMMUNICABLE DISEASE CONTROL:

During Business Hours: (530) 889-7141
After Hours (Nights, Weekends and Holidays): Health Officer Richard J. Burton, M.D., M.P.H., at (530) 889-7119
(In the event that you are unable to reach a Communicable Disease Control Contact, please call the Placer County Office of Emergency Services at (530) 886-5300 or the 24-hour dispatch at (530) 886-5375

I. KEY SUMMARY POINTS

- Highly infectious after aerosolization
- Infectious dose can be as low as 10-15 organisms
- Person-to-person transmission does not occur

Clinical:

- Incubation period is 3-6 days (ranges 1-21 days)
- Aerosolization would most likely result in typhoidal tularemia, with pneumonic involvement
- Typhoidal tularemia is a nonspecific illness, with fever, headache, malaise and non-productive cough (mortality rates can be as high as 30-60%)
- Diagnosis requires high index of suspicion given nonspecific presentation

Laboratory Diagnosis:

- Bacterial cultures should be handled in a Biosafety Level 3 facility; isolation of organism can otherwise put laboratory workers at risk
- Organism is difficult to culture and grows poorly on standard media; cysteine-enriched media is required
- Serology is most commonly used for diagnosis
- Contact Placer County Public Health Laboratory at (530) 889-7205 for assistance.

Patient Isolation:

- Standard precautions. Respiratory isolation not required.

Treatment:

- Streptomycin (7.5 mg/kg IM q 12 hours x 10-14 days) or gentamicin (3-5 mg/kg/day IV or IM qd in 3 divided doses x 10-14 days) are the preferred antibiotics
- Tetracyclines are alternative choices, although they are bacteriostatic and associated with higher relapse rates and must be continued for at least 14 days

Prophylaxis:

- Antibiotic prophylaxis is most effective if begun within 24 hours after exposure to aerosol
- Tetracyclines are recommended for 14 days

ALL SUSPECT CASES OF TULAREMIA MUST BE REPORTED IMMEDIATELY TO THE PLACER COUNTY HEALTH AND HUMAN SERVICES, COMMUNICABLE DISEASE CONTROL:

During Business Hours: (530) 889-7141

After Hours (Nights, Weekends and Holidays): Health Officer Richard J. Burton, M.D., M.P.H., at (530) 889-7119

(In the event that you are unable to reach a Communicable Disease Control Contact, please call the Placer County Office of Emergency Services at (530) 886-5300 or the 24-hour dispatch at (530) 886-5375)

II. Introduction/Epidemiology

Tularemia is a zoonotic disease caused by *Francisella tularensis,* a gram-negative intracellular coccobacillus. *F. tularensis* has several biovars; *F. tularensis* biovar *tularensis* is the most common naturally-occurring isolate in the United States. The organism is primarily recovered from lagomorphs (rabbits), rodents and arthropods (ticks and deer flies) in the United States and from water, mosquitoes and aquatic mammals outside the United States. The rabbit is the vertebrate most commonly associated with tularemia in North

America. In recent years, the reported incidence of tularemia has declined to less than 200 cases per year in the United States.

Tularemia is acquired under natural conditions by direct inoculation (such as an arthropod bite), animal contact such as skinning or eating infected animals, or via the airborne route. (Domestic cats have occasionally transmitted tularemia by bites or scratches.) *F. tularensis* may survive for prolonged periods in water, mud and animal carcasses; even if frozen *Francisella tularensis* is highly infectious. After aerosolization, 10-50 virulent organisms given by aerosol can cause infection in humans, and as few as 10 organisms can cause infection when administered percutaneously. In the event of a bioterrorist attack, aerosolization would be the most likely route of infection.

Tularemia transmission from patient-to-patient has never been reported, even among patients with tularemia pneumonia. Persons exposed to an aerosol of *Francisella tularensis* do not present a risk for secondary infection of others or for re-aerosolization of the organism.

III. **Significance as a Potential Bioterrorist Agent**

- Weaponized by the United States military during the biologic offensive program in the 1950s-1960s.
- Highly infectious after aerosolization; infectious dose can be as low as 10 to 50 microorganisms if inhaled.
- Aerosolized *F. tularensis* would cause typhoidal tularemia (a nonspecific, febrile illness), with high mortality rates (30-60%) if untreated.

IV. **Clinical Manifestations**

During an act of bioterrorism, release of an aerosol will be the most likely route of transmission with typhoidal tularemia the most likely clinical presentation.

There are several different classification systems for clinical tularemia. The most straightforward classifies tularemia into ulceroglandular (75% of patients) and typhoidal (25% of patients). **Ulceroglandular** disease involves lesions on the skin or mucous membranes (including conjunctiva), lymph nodes larger than 1 cm, or both. In **typhoidal** tularemia, the lymph nodes are usually smaller than 1 cm and no skin or mucous membrane lesions are present--this form is more commonly associated with pneumonia and has a higher mortality rate.

A. *Typhoidal Tularemia* -- An acute, nonspecific febrile illness associated with *F. tularensis* that is **not** associated with prominent lymphadenopathy. Typhoidal tularemia is mainly due to inhalation of infected aerosols. **Most likely form during an act of bioterrorism.**

Incubation period: 3 - 6 days (range 1- 21 days)

Symptoms - prominent symptoms include:

- fever with chills
- headache
- myalgias
- sore throat
- anorexia
- nausea
- vomiting
- diarrhea (can be a major component of illness, generally watery stool not bloody)
- abdominal pain
- cough

Patients may develop a sepsis syndrome with hypotension, adult respiratory distress syndrome, renal failure, disseminated intravascular coagulation and shock.

Pleuropulmonary disease (pneumonic tularemia) is common with pulmonary infiltrates or pleural effusions seen in up to 45% of typhoidal tularemia cases. A patchy, alveolar process is most often seen on chest x-ray. Patients may develop acute respiratory distress syndrome and require mechanical ventilation.

B. *Ulceroglandular Tularemia* -- generally due to inoculation of the organism into the skin or mucous membranes.

Incubation period: 3 - 6 days (range 1 - 21 days)

Symptoms - Local papule develops at the inoculation site, with progression to a pustule then an ulcer within several days. Lymphadenopathy develops in 85% of patients. Nodes are usually tender and 0.5-10 cm in diameter (mean 2 cm). Enlarged nodes may become fluctuant, drain spontaneously or persist for months to years.

A cutaneous ulcer occurs in 60% of cases. Ulcers are usually singular and 0.4-3.0 cm in diameter, with heaped-up borders. Ulcers are almost always accompanied by regional lymphadenopathy.

In addition, the following symptoms may be present (in decreasing order of likelihood of appearance):

- fever (present in 85% of patients)
- chills
- headache
- cough
- myalgia
- chest pain
- vomiting
- arthralgia
- sore throat
- abdominal pain
- diarrhea
- dysuria
- back pain
- stiff neck

Ulceroglandular tularemia can also be complicated by pleuropulmonary disease or pharyngeal involvement. Pharyngeal tularemia (via ingestion of contaminated food, water or droplets) is associated with severe throat pain, exudative pharyngitis and often pharyngeal ulcerations.

V. Laboratory Diagnosis

Routine laboratory work must be done in Biosafety Level 2 facilities. However, handling of bacterial cultures once the organism is identified should be done in Biosafety Level 3 facilities If tularemia is suspected, please call the Placer County Public Health Laboratory at (530) 889-7205 to arrange for submission of specimens for testing. After hours, please call Health Officer Richard J. Burton, M.D., M.P.H., at (530) 889-7119.

The diagnosis of tularemia requires a high index of suspicion since the disease often presents with very nonspecific symptoms. The diagnosis can be made by recovery of the organism from blood, ulcers, conjunctival exudates, sputum, pleural fluid, lymph nodes, gastric washings and pharyngeal exudates. Since the organism is difficult to isolate and constitutes a potential danger to laboratory personnel, serologic evidence of infection in a patient with a compatible clinical syndrome is commonly used for diagnosis.

- **Culture**
  F. tularensis grows poorly on standard media. It forms small, smooth, opaque colonies when grown on media containing cysteine or other sulfhydryl compounds (*e.g., glucose cysteine blood agar or thioglycollate broth*) at 37C. The organism has also been isolated from automated radiometric detection systems if the media is subcultured on chocolate agar. The bacteria grows slowly; some strains may require up to 2-3 weeks to develop visible colonies. **Notify the clinical laboratory in advance of submitting specimens for culture which may contain *F. tularensis,* since isolation of the organism can put laboratory workers at risk for infection.**
- **Serology**
  Antibody detection assays include tube agglutination, microagglutination and ELISA. Significant antibody does not appear until the end of the second week of illness, peaks at 4-5 weeks, and can persist for more than a decade. A single titre (by tube agglutination) of > 1:160 is a presumptive positive; a four-fold rise is required for a definitive serologic diagnosis. ELISA and microagglutination tests may be more sensitive than tube agglutination. Antibodies may cross-react with *Brucella* spp., *Proteu*s 0X19 and *Yersinia* spp. but dithiothreitol treatment of the serum will eliminate most of these reactions. Serology testing is available through national reference laboratories.

VI. Handling Laboratory Specimens

Tularemia is the third most commonly reported laboratory-associated bacterial infection. Cases have occurred among clinical laboratorians working with bacterial cultures. Laboratory staff handling specimens from persons who are suspected of having tularemia must wear face masks with eye protection, surgical gloves, protective gowns, and shoe covers --- especially when working with pure bacterial cultures. Laboratory tests (*such as serological examinations and staining of impression smears*) can be performed in Biological Safety Level 2 cabinets.

Blood cultures should be maintained in a closed system and clinical isolates from blood or any other site should be handled in Biological Safety Level 3 cabinets. Every effort should be made to avoid splashing or creating an aerosol. Biosafety Level 3 practices and facilities should be used for inoculation, incubation, centrifugation and harvesting of cell cultures and the manipulation of infected tissues.

Accidental spills of potentially contaminated material should be decontaminated immediately by covering liberally with a disinfectant solution (0.1% sodium hypochlorite or sodium hydroxide (0.1N)). All biohazardous waste should be decontaminated by autoclaving. Contaminated equipment or instruments may be decontaminated with a hypochlorite solution, hydrogen peroxide, peracetic acid, 1% glutaraldehyde solution, formaldehyde, ethylene oxide, copper irradiation, or other O.S.H.A. approved solutions, or by autoclaving or boiling for 10 minutes.

VII. Treatment

The treatment of choice for all forms of tularemia except meningitis is streptomycin; gentamicin is an acceptable alternative. For both drugs, dosages must be adjusted for renal insufficiency. **Gentamicin is safe during pregnancy; avoid streptomycin due to its association with irreversible deafness in children exposed in utero.**

(1) **Streptomycin**: Adult dosage is 0.5-1.0 gm (7.5 mg/kg) intramuscularly every 12 hours for 10-14 days. In very sick patients, streptomycin may be give at 15 mg/kg intramuscularly every 12 hours for 10-14 days.
Pediatric dose: 15 mg/kg intramuscularly every 12 hours for 10-14 days.

Alternatives:
(2) **Gentamicin**: 3-5 mg/kg/day intravenously or intramuscularly in three divided doses, with a peak serum level of at least 5 ug/ml desirable. Continue for 10-14 days.
Pediatric dose: 2.5 mg/kg intravenously or intramuscularly every 8 hours for 10-14 days

(3) Tetracycline and chloramphenicol are bacteriostatic and associated with high relapse rates. These agents must be continued for a minimum of 14 days. **Tetracycline:** 2 grams /day IV or orally in four divided doses or **doxycycline** 100 mg IV or orally twice a day for at least 14 days.
Pediatric dose: [Not recommended for children less than 9 years, pregnant or lactating women] If > 45 kg, give adult dosage of doxycycline; if less than 45 kg, give 2.2 mg/kg twice a day. Tetracycline at 30 mg/kg/day orally, to a maximum of 2 grams/day, in four divided doses for at least 14 days.

Chloramphenicol should generally not be used due to the availability of effective alternatives with fewer serious side effects.

(4) Additional agents with favorable in vitro susceptibility tests but limited clinical data on efficacy include: fluroquinolones (except cinoxacin), erythromycin (resistant strains of *F. tularensis* have been identified), and rifampin. Penicillin and cephalosporins are not effective and should not be used to treat tularemia.

Meningitis
A rare complication of tularemia, meningitis requires special attention with regard to therapy as the penetration of streptomycin or gentamicin into the CSF is suboptimal. The treatment of meningeal infection should include combination therapy with chloramphenicol plus streptomycin or possibly a third-generation cephalosporin plus streptomycin (limited data available on efficacy).

VIII. Isolation of Patients

Tularemia is not transmissible from person-to-person. Standard precautions should be followed for all patients -- **respiratory isolation rooms are not required**. Ulcers or wounds in patients with tularemia should be covered and contact isolation maintained as *F. tularensis* can be isolated from such lesions for one month or longer.

IX. Disposal of Infectious Waste

Use of tracking forms, containment, storage, packaging, treatment and disposal methods should be based upon the same rules as all other regulated medical wastes.

X. Autopsy and Handling of Corpses

All postmortem procedures are to be performed using Respiratory Precautions. Efforts should be made to avoid aerosolization.

- All persons performing or assisting in postmortem procedures must wear mandated P.P.E. (personal protective equipment) as delineated by O.S.H.A. guidelines.
- Instruments should be autoclaved or sterilized with a 10% bleach solution or other solutions approved by O.S.H.A. Surfaces contaminated during postmortem procedures should be decontaminated with an appropriate chemical germicide such as 10% hypochlorite or 5% phenol (carbolic acid).

XI. Management of Exposed Persons

An exposed person is defined as a person who has been exposed to the release of a *Francisella tularensis*-containing aerosol.

- **Post-exposure prophylaxis**: Antibiotic prophylaxis should begin as soon as possible after exposure and is **most effective if begun within 24 hours**. Limited data suggests that tetracyclines may be effective:
  Tetracycline 500 mg orally in 4 divided doses for 14 days
  Doxycycline 100mg orally twice daily for 14 days
- **Pediatric patients and pregnant women**: Although tetracyclines are not generally recommended for children under age 9 or for pregnant women, the risk of developing tularemia may outweigh these limitations. Floroquinolones are a potential alternative for prophylaxis.
  Doxycycline:
- If > 45 kg - 100 mg orally every 12 hours
- If $\leq$ 45 kg - 2.2 mg/kg orally every 12 hours

If antibiotic prophylaxis is not started within 24 hours of exposure, then exposed persons should be instructed to begin a fever watch and seek medical care if temperature exceeds 38.5 ^{o}C.

XII. Reporting to the Health Department

Tularemia is a reportable condition in California. Confirmed or suspect tularemia cases must be reported immediately:

During business hours
Placer County Health and Human Services Communicable Disease Control at (530) 889-7141

After business hours
Placer County Health Officer Richard J. Burton, M.D., M.P.H., at (530) 889-7119

In the event that you are unable to reach a Communicable Disease Control Contact, please call the Placer County Office of Emergency Services at (530) 886-5300 or the 24-hour dispatch at (530) 886-5375

XIII. References

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VIRAL HEMMORHAGIC FEVERS

ALL SUSPECT CASES OF TULAREMIA MUST BE REPORTED IMMEDIATELY TO THE HEALTH AND HUMAN SERVICES COMMUNICABLE DISEASE CONTROL:

During business hours: (530) 889-7141
After hours (Health Officer Richard J. Burton, M.D., M.P.H.): (530) 889-7119

(In the event that you are unable to reach a Communicable Disease Control Contact, please call the Placer County Office of Emergency Services at (530) 886-5300 during business hours, or 24-hour dispatch at (530) 886-5375 after business hours.)

Etiologic Agents: Arenaviradae (Lassa, Junin, Machupo, Guanarito, and Sabia), Filoviradae (Marburg and Ebola), Bunyaviradae (Congo-Crimean hemmorhagic fever virus and hantaviruses)and Flaviradae (yellow fever and Dengue) can all cause viral hemmorhagic fever (VHF)

Epidemiology:

- Highly infectious after aerosolization
- Infectious dose can be as low as 1-10 organisms
- Risk of person-to-person transmission depends on virus

Clinical:

- Incubation period is 4 – 21 days, depending on virus
- Clinical presentation would vary by viral agent; however, dominant clinical features of all are a consequence of microvascular damage and changes in vascular permeability. Fever, myalgia, and prostration may evolve to shock, generalized mucous membrane hemmorhage, and neurologic, hematopoietic, or pulmonary involvement.

Laboratory Diagnosis:

- Viral isolation should be handled in a Biosafety Level 3 or 4 facility and may take 3 – 10 days
- ELISA or reverse transcriptase PCR available for most VHF viruses
- Contact the Placer County Public Health Laboratory for assistance.

Patient Isolation:

- Isolation room with contact precautions.

Treatment:

- Ribavirin (30 mg/kg IV x 1, then 15 mg/kg IV q 6 h x 4 days, 7.5 mg/kg IV q 8 x 6 days) may be helpful for Congo-Crimean hemmorhagic fever or arenaviruses

Prophylaxis:

- Licensed vaccine available only for yellow fever

PLACER COUNTY

HEALTH AND HUMAN SERVICES

COMMUNICABLE DISEASE CONTROL

Medical Treatment and Response to Suspected Q-Fever: Information for Health Care Providers During Biologic Emergencies

ALL SUSPECT CASES OF Q FEVER MUST BE REPORTED IMMEDIATELY TO THE PLACER COUNTY HEALTH AND HUMAN SERVICES, COMMUNICABLE DISEASE CONTROL:

During Business Hours: (530) 889-7141

After Hours (Nights, Weekends and Holidays): Health Officer Richard J. Burton, M.D., M.P.H., at (530) 889-7119

(In the event that you are unable to reach a Communicable Disease Control Contact, please call the Placer County Office of Emergency Services at (530) 886-5300 or the 24-hour dispatch at (530) 886-5375)

I. KEY SUMMARY POINTS

Epidemiology:

- *Coxiella burnettii* is highly infectious by the aerosol route
- Q Fever is **rarely** transmitted from person to person

Clinical:

- Incubation period is 10-40 days
- Acute infection may be asymptomatic or a self-limited febrile illness
- Chest x-ray evidence of pneumonia is present in up to 50% of cases
- Mortality rate is less than 2%
- Contact the Placer County Public Health Laboratory at (530) 8889-7141 for assistance.

Diagnosis:

- Requires serologic confirmation (IFA or ELISA)
- Isolation of organism is not recommended due to significant hazards from handling bacterial cultures in the laboratory

Treatment:

- Illness usually resolves **without** treatment
- Tetracyclines are the antibiotics of choice for more severe illnesses

Prophylaxis:

- Tetracycline antibiotics are very effective if administered **8 to 12 days AFTER exposure**
- Starting prophylaxis immediately after exposure can delay symptom onset but does not prevent illness

Patient Isolation:

- Universal precautions. Patients do **not** require isolation rooms

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II. Introduction/Epidemiology

Q fever is a zoonotic disease caused by *Coxiella burnetii,* a rickettsia-like organism. *C. burnetii* is unable to replicate outside host cells, but there is a spore-like form of the organism that is extremely resistant to heat, dessication and many standard antiseptic compounds. The organism can persist in the environment for long periods under harsh conditions. Despite the inherent resilience of *C. burnetii* and its ease in transmissibility, generally by inhaled aerosols, the acute clinical disease of Q fever is usually benign, although temporarily incapacitating.

Coxiella burnetii is extremely infectious. Humans have been infected most commonly by contact with domestic livestock, particularly goats, cattle and sheep but household pets, notably cats, have also been associated with infection. The risk is highest when humans are exposed to these animals at parturition, presumably via aerosolization of the organism from the uterus during birthing. *Coxiella* organisms can persist in the local environment, and produce infection, for weeks or months after contamination.

Q fever has VERY RARELY been transmitted from person-to-person (specifically, transmission has occurred to attendants during autopsies and from an infected patient to the attending obstetrician during delivery). **Persons exposed to an aerosol of *Coxiella burnetii* do not present a risk for secondary transmission to others or for re-aerosolization of the organism.**

III. Significance as a Potential Bioterrorist Agent

- The spore-like form of the organism is resistant to heat and dessication, and can persist in the environment for long periods of time.

- Highly infectious when aerosolized and inhaled; a single organism may cause clinical illness

- Aerosolized *Coxiella burnetii* can result in an incapacitating respiratory illness; however, severe illness and fatalities are rare.

IV. Clinical Manifestations

During an act of bioterrorism, release of an aerosol will be the most likely route of transmission.

A. Acute Q Fever

Incubation period - 10 - 40 days, duration of the incubation period is inversely correlated with the size of the inoculum.

Symptoms - Acute disease is **not** clinically distinct, and illness resembles viral respiratory infections or atypical pneumonias. Can be divided into 3 main categories: (1) asymptomatic infection (seroconversion) - occurs in up to 50% of exposed persons, (2) self-limited febrile flu-like illness without pneumonia lasting 2 to 14 days and (3) pneumonia. Hepatitis, meningo-encephalitis, myocarditis, and pericarditis may be present acutely but are relatively uncommon.

Symptomatic patients exhibit any combination of the following (in order of decreasing frequency of appearance):

SYMPTOM	RELATIVE FREQUENCY (%)
fever (present in all symptomatic patients)	80-100
chills, rigors	75-100
severe headache, **retroorbital pain (may be a useful clue to diagnosis)**	50-100
fatigue, anorexia, weight loss	50-85
cough	50-60
myalgia	45-84
pleuritic chest pain	40-50
nausea, vomiting	15-20
diarrhea	5-20
neck stiffness	5-7

Pneumonia -Chest x-ray evidence of pneumonia may be present in up to 50% of patients. There are three possible presentations: (a) atypical pneumonia (dry

nonproductive cough) (b) rapidly progressive pneumonia (often mimicking Legionnaire's disease), or (c) pneumonia with fever but no pulmonary symptoms [most common clinical scenario for acute Q fever]. *Radiographic findings*: Variable; may have pleural-based opacities, multiple rounded opacities, about 35% have pleural effusion, hilar adenopathy is uncommon.

Duration - 2 days - 2 weeks

Mortality - Low, estimated to be about 2% (usually in patients with co-morbid conditions)

B. Chronic Q Fever

Chronic infection due to Q fever is uncommon, occurring in less than 1% of acute infections. Endocarditis is the usual manifestation of Q fever but a wide array of syndromes have been described including: infection of vascular grafts, osteomyelitis, infectious arthritis, chronic hepatitis, pseudotumor of the lung, chronic pulmonary fibrosis, infection during pregnancy with miscarriage and prolonged fever.

Incubation period - varies, can be months to several years

Symptoms - Variable depending on specific clinical syndrome. Most often diagnosed in patients with either a cardiovascular abnormality (valvulopathy, prosthesis or aneurysm) or an underlying immunocompromised state (i.e., HIV infection or cancer).

Laboratory Diagnosis

ALL SUSPECT CASES OF Q FEVER MUST BE REPORTED IMMEDIATELY TOTHE PLACER COUNTY HEALTH AND HUMAN SERVICES, COMMUNICABLE DISEASE CONTROL:

During Business Hours: (530) 889-7141

After Hours (Nights, Weekends and Holidays): Health Officer Richard J. Burton, M.D., M.P.H., at (530) 889-7119

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The diagnosis of Q Fever requires a high index of suspicion since the disease often presents with nonspecific symptoms which can be difficult to distinguish from viral illnesses or atypical pneumonia. The diagnosis is generally confirmed serologically; most laboratories are not equipped to isolate *Coxiella burnetii* and isolation of the organism is not recommended due to the significant hazards from handling bacterial cultures in the laboratory.

- **Serology**
  Several assays are available; antibody detection by indirect fluorescent antibody (IFA) or ELISA are used most commonly and appear to be the most sensitive. Significant IgM antibody does not appear until 2-3 weeks into illness and may persist for years. Acute and convalescent (2-3 months after onset of illness) antibody titres show a four-fold rise. In acute Q fever, antibodies to phase II antigens are higher than those to phase I antigens, in chronic Q fever the reverse occurs. Antibodies of the IgM type are usually observed for the first 6-12 months after infection, with IgG persisting afterward.
- **Contact the Placer County Public Health Laboratory at (530) 889-7205 for assistance.**

V. Handling Laboratory Specimens

Laboratory staff handling specimens from persons who might have Q fever must wear surgical gloves, protective gowns, and shoe covers. Laboratory tests, such as serological examinations and staining of tissue impression smears, can be performed in Biological Safety Level 2 cabinets; although not recommended, blood cultures should be maintained in a closed system. Every effort should be made to avoid splashing or creating an aerosol. Biosafety Level 3 practices and facilities should be used for inoculation, incubation and harvesting of cell cultures and the manipulation of infected tissues.

Accidental spills of potentially contaminated material should be decontaminated immediately by covering liberally with a disinfectant solution (0.05% hypochlorite, 5% peroxide, or 1:100 solution of Lysol). All biohazardous waste should be decontaminated by autoclaving. Contaminated equipment or instruments may be decontaminated with a hypochlorite solution, hydrogen peroxide, peracetic acid, 1% glutaraldehyde solution, formaldehyde, ethylene oxide, copper irradiation, or other O.S.H.A. approved solutions, or by autoclaving or boiling for 10 minutes.

VI. Treatment

A. Acute Q Fever

Pneumonia usually resolves without treatment in 15 days; therefore, in the event of a bioterrorist attack, therapy may only be required for persons with more severe illness. Several antibiotics have been evaluated as therapeutic agents for acute Q fever -- tetracyclines have been shown to shorten the duration of illness and are considered the **drug of choice**, particularly for severe infection:

- ***Adult dosages:***
  Doxycycline 100 mg every 12 hours po or IV for 15-21 days or **tetracycline** 500 mg po every 6 hours for 15-21 days. (**NOTE:** For milder illnesses, 5-7 days of therapy may be sufficient)

  Alternatives:
  Quinolones, chloramphenicol, trimethroprim-sulfamethoxazole are also probably effective.

  Studies of erythromycin (500 mg - 1 gram every 6 hours p.o. or IV) have shown conflicting results, and erythromycin is probably not preferred for cases of severe pneumonia. Azithromycin appears to be another option but little clinical information is available. Beta-lactam antibiotics are generally ineffective.

- ***Pediatric dosages:***
  For more severe illnesses, when benefits outweigh the risks, consider use of doxycycline (or co-trimoxazole or chloramphenicol).

If > or = 8 years of age:	**Doxycycline:**	
		If > 45 kg - 100 mg IV or po every 12 hours
		If < 45 kg - 2.2 mg/kg IV or po every 12 hours
If < 8 years of age:	**Co-trimoxazole**	4 mg/kg IV or orally every 12 hours
	Chloramphenicol	25 mg/kg orally every 12 hours
Newborns up to age 2 months:	**Ciprofloxacin**	10-20 mg/kg orally twice daily, do not exceed 1 gram/day.

- ***Pregnant Women Post-Exposure Prophylaxis*** - Co-trimoxazole [1 DS tablet orally twice daily], is the preferred antibiotic, except at term, when the risk of kernicteris is greatest -- use fluoroquinolones [ciprofloxacin 500 mg orally twice daily]

B. Chronic Q Fever

Endocarditis requires combination therapy, usually with doxycycline plus rifampin or possibly a quinolone plus rifampin. The duration of therapy is for years and a valve replacement is often necessary.

VII. Isolation of Patients

Q fever is not transmissible from person-to-person. Standard precautions should be followed for all patients. Respiratory isolation rooms are not required.

VIII. Disposal of Infectious Waste

Use of tracking forms, containment, storage, packaging, treatment and disposal methods should be based upon the same rules as all other regulated medical wastes.

IX. Autopsy and Handling of Corpses

All postmortem procedures are to be performed using Respiratory Precautions. Efforts should be made to avoid aerosolization.

- All persons performing or assisting in postmortem procedures must wear mandated P.P.E. (personal protective equipment) as delineated by O.S.H.A. guidelines.

- Instruments should be autoclaved or sterilized with a 10% bleach solution or other solutions approved by O.S.H.A. Surfaces contaminated during postmortem procedures should be decontaminated with an appropriate chemical germicide such as 10% hypochlorite or 5% phenol (carbolic acid).

X. Management of Exposed Persons

An exposed person is defined as a person who has been exposed to the release of a *Coxiella burnetii* containing aerosol.

Post-exposure prophylaxis: Antibiotic prophylaxis is very effective and will prevent clinical disease **if administered 8-12 days AFTER exposure** (doxycycline 100 mg po every 12 hours or tetracycline 500 mg po every 6 hours) for 5 days. **Starting prophylaxis immediately after exposure can delay onset of disease but not prevent symptoms from occurring.**

Pediatric Post-Exposure Prophylaxis with Doxycycline:

If > or = 8 years of age:	If > 45 kg - 100 mg orally every 12 hours for 5 days If < 45 kg - 2.2 mg/kg orally every 12 hours for 5 days	
If < 8 years of age:	**Co-trimoxazole**	4 mg/kg orally every 12 hours for 5 days
	Chloramphenicol	25 mg/kg orally every 12 hours for 5 days
Newborns up to age 2 months:	**Ciprofloxacin**	10-20 mg/kg orally twice daily for 5 days, do not exceed 1 gram/day

XI. **Reporting to the Health Department**

Confirmed or suspect Q Fever cases must be reported immediately to the Placer County Health and Human Services Communicable Disease Control:

- **During business hours**
  Placer County Health and Human Services Communicable Disease Control at (530) 889-7141

- **After business hours**
  Placer County Health Officer Richard J. Burton, M.D., M.P.H., at (530) 889-7119

- In the event that you are unable to reach a Communicable Disease Control Contact, please call the Placer County Office of Emergency Services at (530) 886-5300 or the 24-hour dispatch at (530) 886-5375

XII. **References**

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WEEKLY REPORT

Recommendations and Reports

Inside: Continuing Education Examination

Biological and Chemical Terrorism: Strategic Plan for Preparedness and Response

Recommendations of the CDC Strategic Planning Workgroup

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Centers for Disease Control and Prevention (CDC)
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Biological and Chemical Terrorism: Strategic Plan for Preparedness and Response

Recommendations of the CDC Strategic Planning Workgroup

". . . and he that will not apply new remedies must expect new evils; for time is the greatest innovator. . . ."

–The Essays by Sir Francis Bacon, 1601

Summary

The U.S. national civilian vulnerability to the deliberate use of biological and chemical agents has been highlighted by recognition of substantial biological weapons development programs and arsenals in foreign countries, attempts to acquire or possess biological agents by militants, and high-profile terrorist attacks. Evaluation of this vulnerability has focused on the role public health will have detecting and managing the probable covert biological terrorist incident with the realization that the U.S. local, state, and federal infrastructure is already strained as a result of other important public health problems. In partnership with representatives for local and state health departments, other federal agencies, and medical and public health professional associations, CDC has developed a strategic plan to address the deliberate dissemination of biological or chemical agents. The plan contains recommendations to reduce U.S. vulnerability to biological and chemical terrorism — preparedness planning, detection and surveillance, laboratory analysis, emergency response, and communication systems. Training and research are integral components for achieving these recommendations. Success of the plan hinges on strengthening the relationships between medical and public health professionals and on building new partnerships with emergency management, the military, and law enforcement professionals.

INTRODUCTION

An act of biological or chemical terrorism might range from dissemination of aerosolized anthrax spores to food product contamination, and predicting when and how such an attack might occur is not possible. However, the possibility of biological or chemical terrorism should not be ignored, especially in light of events during the past 10 years (e.g., the sarin gas attack in the Tokyo subway [*1*] and the discovery of military bioweapons programs in Iraq and the former Soviet Union [*2*]). Preparing the nation to address this threat is a formidable challenge, but the consequences of being unprepared could be devastating.

The public health infrastructure must be prepared to prevent illness and injury that would result from biological and chemical terrorism, especially a covert terrorist attack. As with emerging infectious diseases, early detection and control of biological or chemical attacks depends on a strong and flexible public health system at the local, state, and federal levels. In addition, primary health-care providers throughout the United States must be vigilant because they will probably be the first to observe and report unusual illnesses or injuries.

This report is a summary of the recommendations made by CDC's Strategic Planning Workgroup in *Preparedness and Response to Biological and Chemical Terrorism: A Strategic Plan* (*CDC, unpublished report, 2000*), which outlines steps for strengthening public health and health-care capacity to protect the United States against these dangers. This strategic plan marks the first time that CDC has joined with law enforcement, intelligence, and defense agencies in addition to traditional CDC partners to address a national security threat.

As a reflection of the need for broad-based public health involvement in terrorism preparedness and planning, staff from CDC's centers, institute, and offices participated in developing the strategic plan, including the

- National Center for Infectious Diseases,
- National Center for Environmental Health,
- Public Health Practice Program Office,
- Epidemiology Program Office,
- National Institute for Occupational Safety and Health,
- Office of Health and Safety,
- National Immunization Program, and
- National Center for Injury Prevention and Control.

The Agency for Toxic Substances and Disease Registry (ATSDR) is also participating with CDC in this effort and will provide expertise in the area of industrial chemical terrorism. In this report, the term *CDC* includes ATSDR when activities related to chemical terrorism are discussed. In addition, colleagues from local, state, and federal agencies; emergency medical services (EMS); professional societies; universities and medical centers; and private industry provided suggestions and constructive criticism.

Combating biological and chemical terrorism will require capitalizing on advances in technology, information systems, and medical sciences. Preparedness will also require a re-examination of core public health activities (e.g., disease surveillance) in light of these advances. Preparedness efforts by public health agencies and primary health-care providers to detect and respond to biological and chemical terrorism will have the added benefit of strengthening the U.S. capacity for identifying and controlling injuries and emerging infectious diseases.

U.S. VULNERABILITY TO BIOLOGICAL AND CHEMICAL TERRORISM

Terrorist incidents in the United States and elsewhere involving bacterial pathogens (*3*), nerve gas (*1*), and a lethal plant toxin (i.e., ricin) (*4*), have demonstrated that the United States is vulnerable to biological and chemical threats as well as explosives. Recipes for preparing "homemade" agents are readily available (*5*), and reports of arsenals of military bioweapons (*2*) raise the possibility that terrorists might have access to highly dangerous agents, which have been engineered for mass dissemination as small-particle aerosols. Such agents as the variola virus, the causative agent of smallpox, are highly contagious and often fatal. Responding to large-scale outbreaks caused

by these agents will require the rapid mobilization of public health workers, emergency responders, and private health-care providers. Large-scale outbreaks will also require rapid procurement and distribution of large quantities of drugs and vaccines, which must be available quickly.

OVERT VERSUS COVERT TERRORIST ATTACKS

In the past, most planning for emergency response to terrorism has been concerned with overt attacks (e.g., bombings). Chemical terrorism acts are likely to be overt because the effects of chemical agents absorbed through inhalation or by absorption through the skin or mucous membranes are usually immediate and obvious. Such attacks elicit immediate response from police, fire, and EMS personnel.

In contrast, attacks with biological agents are more likely to be covert. They present different challenges and require an additional dimension of emergency planning that involves the public health infrastructure (Box 1). Covert dissemination of a biological agent in a public place will not have an immediate impact because of the delay between exposure and onset of illness (i.e., the incubation period). Consequently, the first casualties of a covert attack probably will be identified by physicians or other primary health-care providers. For example, in the event of a covert release of the contagious variola virus, patients will appear in doctors' offices, clinics, and emergency rooms during the first or second week, complaining of fever, back pain, headache, nausea, and other symptoms of what initially might appear to be an ordinary viral infection. As the disease progresses, these persons will develop the papular rash characteristic of early-stage smallpox, a rash that physicians might not recognize immediately. By the time the rash becomes pustular and patients begin to die, the terrorists would be far away and the disease disseminated through the population by person-to-person contact. Only a short window of opportunity will exist between the time the first cases are identified and a second wave of the population becomes ill. During that brief period, public health officials will need to determine that an attack has occurred, identify the organism, and prevent more casualties through prevention strategies (e.g., mass vaccination or prophylactic treatment). As person-to-person contact continues, successive waves of transmission could carry infection to other worldwide localities. These issues might also be relevant for other person-to-person transmissible etiologic agents (e.g., plague or certain viral hemorrhagic fevers).

BOX 1. Local public health agency preparedness

- Because the initial detection of a covert biological or chemical attack will probably occur at the local level, disease surveillance systems at state and local health agencies must be capable of detecting unusual patterns of disease or injury, including those caused by unusual or unknown threat agents.
- Because the initial response to a covert biological or chemical attack will probably be made at the local level, epidemiologists at state and local health agencies must have expertise and resources for responding to reports of clusters of rare, unusual, or unexplained illnesses.

Certain chemical agents can also be delivered covertly through contaminated food or water. In 1999, the vulnerability of the food supply was illustrated in Belgium, when

chickens were unintentionally exposed to dioxin-contaminated fat used to make animal feed (*6*). Because the contamination was not discovered for months, the dioxin, a cancer-causing chemical that does not cause immediate symptoms in humans, was probably present in chicken meat and eggs sold in Europe during early 1999. This incident underscores the need for prompt diagnoses of unusual or suspicious health problems in animals as well as humans, a lesson that was also demonstrated by the recent outbreak of mosquitoborne West Nile virus in birds and humans in New York City in 1999. The dioxin episode also demonstrates how a covert act of foodborne biological or chemical terrorism could affect commerce and human or animal health.

FOCUSING PREPAREDNESS ACTIVITIES

Early detection of and response to biological or chemical terrorism are crucial. Without special preparation at the local and state levels, a large-scale attack with variola virus, aerosolized anthrax spores, a nerve gas, or a foodborne biological or chemical agent could overwhelm the local and perhaps national public health infrastructure. Large numbers of patients, including both infected persons and the "worried well," would seek medical attention, with a corresponding need for medical supplies, diagnostic tests, and hospital beds. Emergency responders, health-care workers, and public health officials could be at special risk, and everyday life would be disrupted as a result of widespread fear of contagion.

Preparedness for terrorist-caused outbreaks and injuries is an essential component of the U.S. public health surveillance and response system, which is designed to protect the population against any unusual public health event (e.g., influenza pandemics, contaminated municipal water supplies, or intentional dissemination of *Yersinia pestis* , the causative agent of plague [*7*]). The epidemiologic skills, surveillance methods, diagnostic techniques, and physical resources required to detect and investigate unusual or unknown diseases, as well as syndromes or injuries caused by chemical accidents, are similar to those needed to identify and respond to an attack with a biological or chemical agent. However, public health agencies must prepare also for the special features a terrorist attack probably would have (e.g., mass casualties or the use of rare agents) (Boxes 2–5). Terrorists might use combinations of these agents, attack in more than one location simultaneously, use new agents, or use organisms that are not on the critical list (e.g., common, drug-resistant, or genetically engineered pathogens). Lists of critical biological and chemical agents will need to be modified as new information becomes available. In addition, each state and locality will need to adapt the lists to local conditions and preparedness needs by using the criteria provided in CDC's strategic plan.

Potential biological and chemical agents are numerous, and the public health infrastructure must be equipped to quickly resolve crises that would arise from a biological or chemical attack. However, to best protect the public, the preparedness efforts must be focused on agents that might have the greatest impact on U.S. health and security, especially agents that are highly contagious or that can be engineered for widespread dissemination via small-particle aerosols. Preparing the nation to address these dangers is a major challenge to U.S. public health systems and health-care providers. Early detection requires increased biological and chemical terrorism awareness among frontline health-care providers because they are in the best position to report suspicious illnesses and injuries. Also, early detection will require improved communication systems between those providers and public health officials. In addition, state and local

health-care agencies must have enhanced capacity to investigate unusual events and unexplained illnesses, and diagnostic laboratories must be equipped to identify biological and chemical agents that rarely are seen in the United States. Fundamental to these efforts is comprehensive, integrated training designed to ensure core competency in public health preparedness and the highest levels of scientific expertise among local, state, and federal partners.

BOX 2. Preparing public health agencies for biological attacks

Steps in Preparing for Biological Attacks

- Enhance epidemiologic capacity to detect and respond to biological attacks.
- Supply diagnostic reagents to state and local public health agencies.
- Establish communication programs to ensure delivery of accurate information.
- Enhance bioterrorism-related education and training for health-care professionals.
- Prepare educational materials that will inform and reassure the public during and after a biological attack.
- Stockpile appropriate vaccines and drugs.
- Establish molecular surveillance for microbial strains, including unusual or drug-resistant strains.
- Support the development of diagnostic tests.
- Encourage research on antiviral drugs and vaccines.

BOX 3. Critical biological agents

Category A

The U.S. public health system and primary health-care providers must be prepared to address varied biological agents, including pathogens that are rarely seen in the United States. High-priority agents include organisms that pose a risk to national security because they

- can be easily disseminated or transmitted person-to-person;
- cause high mortality, with potential for major public health impact;
- might cause public panic and social disruption; and
- require special action for public health preparedness (Box 2).

Category A agents include

- variola major (smallpox);
- *Bacillus anthracis* (anthrax);
- *Yersinia pestis* (plague);
- *Clostridium botulinum* toxin (botulism);
- *Francisella tularensis* (tularaemia);
- filoviruses,
  - — Ebola hemorrhagic fever,
  - — Marburg hemorrhagic fever; and
- arenaviruses,
  - — Lassa (Lassa fever),
  - — Junin (Argentine hemorrhagic fever) and related viruses.

BOX 3. (*Continued*) Critical biological agents

Category B

Second highest priority agents include those that

- are moderately easy to disseminate;
- cause moderate morbidity and low mortality; and
- require specific enhancements of CDC's diagnostic capacity and enhanced disease surveillance.

Category B agents include

- *Coxiella burnetti* (Q fever);
- *Brucella* species (brucellosis);
- *Burkholderia mallei* (glanders);
- alphaviruses,
  - — Venezuelan encephalomyelitis,
  - — eastern and western equine encephalomyelitis;
- ricin toxin from *Ricinus communis* (castor beans);
- epsilon toxin of *Clostridium perfringens*; and
- *Staphylococcus* enterotoxin B.

A subset of List B agents includes pathogens that are food- or waterborne. These pathogens include but are not limited to

- *Salmonella* species,
- *Shigella dysenteriae*,
- *Escherichia coli* O157:H7,
- *Vibrio cholerae*, and
- *Cryptosporidium parvum*.

Category C

Third highest priority agents include emerging pathogens that could be engineered for mass dissemination in the future because of

- availability;
- ease of production and dissemination; and
- potential for high morbidity and mortality and major health impact.

Category C agents include

- Nipah virus,
- hantaviruses,
- tickborne hemorrhagic fever viruses,
- tickborne encephalitis viruses,
- yellow fever, and
- multidrug-resistant tuberculosis.

Preparedness for List C agents requires ongoing research to improve disease detection, diagnosis, treatment, and prevention. Knowing in advance which newly emergent pathogens might be employed by terrorists is not possible; therefore, linking bioterrorism preparedness efforts with ongoing disease surveillance and outbreak response activities as defined in CDC's emerging infectious disease strategy is imperative.*

*CDC. Preventing emerging infectious diseases: a strategy for the 21st century. Atlanta, Georgia: U.S. Department of Health and Human Services, 1998.

BOX 4. Preparing public health agencies for chemical attacks

Steps in Preparing for Chemical Attacks

- Enhance epidemiologic capacity for detecting and responding to chemical attacks.
- Enhance awareness of chemical terrorism among emergency medical service personnel, police officers, firefighters, physicians, and nurses.
- Stockpile chemical antidotes.
- Develop and provide bioassays for detection and diagnosis of chemical injuries.
- Prepare educational materials to inform the public during and after a chemical attack

BOX 5. Chemical agents

Chemical agents that might be used by terrorists range from warfare agents to toxic chemicals commonly used in industry. Criteria for determining priority chemical agents include

- chemical agents already known to be used as weaponry;
- availability of chemical agents to potential terrorists;
- chemical agents likely to cause major morbidity or mortality;
- potential of agents for causing public panic and social disruption; and
- agents that require special action for public health preparedness (Box 4).

Categories of chemical agents include

- nerve agents,
  - — tabun (ethyl N,N-dimethylphosphoramidocyanidate),
  - — sarin (isopropyl methylphosphanofluoridate),
  - — soman (pinacolyl methyl phosphonofluoridate),
  - — GF (cyclohexylmethylphosphonofluoridate),
  - — VX (o-ethyl-[S]-[2-diisopropylaminoethyl]-methylphosphonothiolate);
- blood agents,
  - — hydrogen cyanide,
  - — cyanogen chloride;
- blister agents,
  - — lewisite (an aliphatic arsenic compound, 2-chlorovinyldichloroarsine),
  - — nitrogen and sulfur mustards,
  - — phosgene oxime;
- heavy metals,
  - — arsenic,
  - — lead,
  - — mercury;
- Volatile toxins,
  - — benzene,
  - — chloroform,
  - — trihalomethanes;

BOX 5. ***(Continued)*** **Chemical agents**

- pulmonary agents,
  - — phosgene,
  - — chlorine,
  - — vinyl chloride;
- incapacitating agents,
  - — BZ (3-quinuclidinyl benzilate);
- pesticides, persistent and nonpersistent;
- dioxins, furans, and polychlorinated biphenyls (PCBs);
- explosive nitro compounds and oxidizers,
  - — ammonium nitrate combined with fuel oil;
- flammable industrial gases and liquids,
  - — gasoline,
  - — propane;
- poison industrial gases, liquids, and solids,
  - — cyanides,
  - — nitriles; and
- corrosive industrial acids and bases,
  - — nitric acid,
  - — sulfuric acid.

Because of the hundreds of new chemicals introduced internationally each month, treating exposed persons by clinical syndrome rather than by specific agent is more useful for public health planning and emergency medical response purposes. Public health agencies and first responders might render the most aggressive, timely, and clinically relevant treatment possible by using treatment modalities based on syndromic categories (e.g., burns and trauma, cardiorespiratory failure, neurologic damage, and shock). These activities must be linked with authorities responsible for environmental sampling and decontamination.

KEY FOCUS AREAS

CDC's strategic plan is based on the following five focus areas, with each area integrating training and research:

- preparedness and prevention;
- detection and surveillance;
- diagnosis and characterization of biological and chemical agents;
- response; and
- communication.

Preparedness and Prevention

Detection, diagnosis, and mitigation of illness and injury caused by biological and chemical terrorism is a complex process that involves numerous partners and activities. Meeting this challenge will require special emergency preparedness in all cities and

states. CDC will provide public health guidelines, support, and technical assistance to local and state public health agencies as they develop coordinated preparedness plans and response protocols. CDC also will provide self-assessment tools for terrorism preparedness, including performance standards, attack simulations, and other exercises. In addition, CDC will encourage and support applied research to develop innovative tools and strategies to prevent or mitigate illness and injury caused by biological and chemical terrorism.

Detection and Surveillance

Early detection is essential for ensuring a prompt response to a biological or chemical attack, including the provision of prophylactic medicines, chemical antidotes, or vaccines. CDC will integrate surveillance for illness and injury resulting from biological and chemical terrorism into the U.S. disease surveillance systems, while developing new mechanisms for detecting, evaluating, and reporting suspicious events that might represent covert terrorist acts. As part of this effort, CDC and state and local health agencies will form partnerships with front-line medical personnel in hospital emergency departments, hospital care facilities, poison control centers, and other offices to enhance detection and reporting of unexplained injuries and illnesses as part of routine surveillance mechanisms for biological and chemical terrorism.

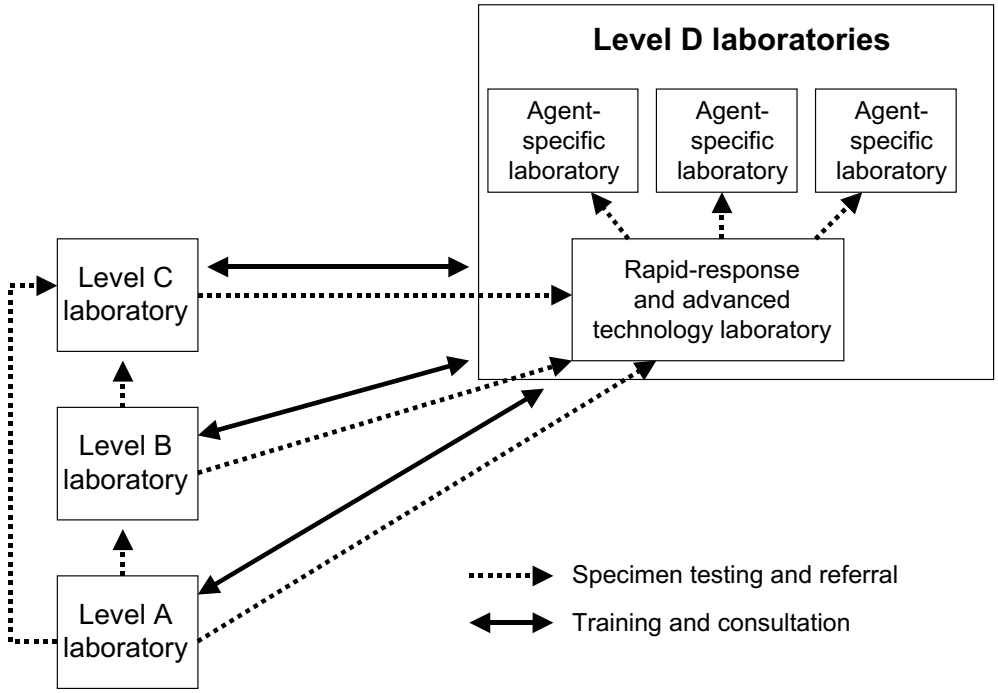
Diagnosis and Characterization of Biological and Chemical Agents

CDC and its partners will create a multilevel laboratory response network for bioterrorism (LRNB). That network will link clinical labs to public health agencies in all states, districts, territories, and selected cities and counties and to state-of-the-art facilities that can analyze biological agents (Figure 1). As part of this effort, CDC will transfer diagnostic technology to state health laboratories and others who will perform initial testing. CDC will also create an in-house rapid-response and advanced technology (RRAT) laboratory. This laboratory will provide around-the-clock diagnostic confirmatory and reference support for terrorism response teams. This network will include the regional chemical laboratories for diagnosing human exposure to chemical agents and provide links with other departments (e.g., the U.S. Environmental Protection Agency, which is responsible for environmental sampling).

Response

A comprehensive public health response to a biological or chemical terrorist event involves epidemiologic investigation, medical treatment and prophylaxis for affected persons, and the initiation of disease prevention or environmental decontamination measures. CDC will assist state and local health agencies in developing resources and expertise for investigating unusual events and unexplained illnesses. In the event of a confirmed terrorist attack, CDC will coordinate with other federal agencies in accord with Presidential Decision Directive (PDD) 39. PDD 39 designates the Federal Bureau of Investigation as the lead agency for the crisis plan and charges the Federal Emergency Management Agency with ensuring that the federal response management is adequate to respond to the consequences of terrorism (8). If requested by a state health agency, CDC will deploy response teams to investigate unexplained or suspicious illnesses or

FIGURE 1. Multilevel laboratory response network for bioterrorism that will link clinical labs to public health agencies



Functional Levels of the Laboratory Response Network for Bioterrorism

Level A: Early detection of intentional dissemination of biological agents — Level A laboratories will be public health and hospital laboratories with low-level biosafety facilities. Level A laboratories will use clinical data and standard microbiological tests to decide which specimens and isolates should be forwarded to higher level biocontainment laboratories. Level A laboratory staff will be trained in the safe collection, packaging, labeling, and shipping of samples that might contain dangerous pathogens.

Level B: Core capacity for agent isolation and presumptive-level testing of suspect specimens — Level B laboratories will be state and local public health agency laboratories that can test for specific agents and forward organisms or specimens to higher level biocontainment laboratories. Level B laboratories will minimize false positives and protect Level C laboratories from overload. Ultimately, Level B laboratories will maintain capacity to perform confirmatory testing and characterize drug susceptibility.

Level C: Advanced capacity for rapid identification — Level C laboratories, which could be located at state health agencies, academic research centers, or federal facilities, will perform advanced and specialized testing. Ultimately, Level C laboratories will have the capacity to perform toxicity testing and employ advanced diagnostic technologies (e.g., nucleic acid amplification and molecular fingerprinting). Level C laboratories will participate in the evaluation of new tests and reagents and determine which assays could be transferred to Level B laboratories.

Level D: Highest level containment and expertise in the diagnosis of rare and dangerous biological agents — Level D laboratories will be specialized federal laboratories with unique experience in diagnosis of rare diseases (e.g., smallpox and Ebola). Level D laboratories also will develop or evaluate new tests and methods and have the resources to maintain a strain bank of biological agents. Level D laboratories will maintain the highest biocontainment facilities and will be able to conduct all tests performed in Level A, B, and C laboratories, as well as additional confirmatory testing and characterization, as needed. They will also have the capacity to detect genetically engineered agents.

unusual etiologic agents and provide on-site consultation regarding medical management and disease control. To ensure the availability, procurement, and delivery of medical supplies, devices, and equipment that might be needed to respond to terrorist-caused illness or injury, CDC will maintain a national pharmaceutical stockpile.

Communication Systems

U.S. preparedness to mitigate the public health consequences of biological and chemical terrorism depends on the coordinated activities of well-trained health-care and public health personnel throughout the United States who have access to up-to-the minute emergency information. Effective communication with the public through the news media will also be essential to limit terrorists' ability to induce public panic and disrupt daily life. During the next 5 years, CDC will work with state and local health agencies to develop a) a state-of-the-art communication system that will support disease surveillance; b) rapid notification and information exchange regarding disease outbreaks that are possibly related to bioterrorism; c) dissemination of diagnostic results and emergency health information; and d) coordination of emergency response activities. Through this network and similar mechanisms, CDC will provide terrorism-related training to epidemiologists and laboratorians, emergency responders, emergency department personnel and other front-line health-care providers, and health and safety personnel.

PARTNERSHIPS AND IMPLEMENTATION

Implementation of the objectives outlined in CDC's strategic plan will be coordinated through CDC's Bioterrorism Preparedness and Response Program. Program personnel are charged with a) helping build local and state preparedness, b) developing U.S. expertise regarding potential threat agents, and c) coordinating response activities during actual bioterrorist events. Program staff have established priorities for 2000–2002 regarding the focus areas (Box 6).

Implementation will require collaboration with state and local public health agencies, as well as with other persons and groups, including

- public health organizations,
- medical research centers,
- health-care providers and their networks,
- professional societies,
- medical examiners,
- emergency response units and responder organizations,
- safety and medical equipment manufacturers,
- the U.S. Office of Emergency Preparedness and other Department of Health and Human Services agencies,
- other federal agencies, and
- international organizations.

BOX 6. Implementation Priorities Regarding Focus Areas for 2000–2002

Preparedness and Prevention

- Maintain a public health preparedness and response cooperative agreement that provides support to state health agencies who are working with local agencies in developing coordinated bioterrorism plans and protocols.
- Establish a national public health distance-learning system that provides biological and chemical terrorism preparedness training to health-care workers and to state and local public health workers.
- Disseminate public health guidelines and performance standards on biological and chemical terrorism preparedness planning for use by state and local health agencies.

Detection and Surveillance

- Strengthen state and local surveillance systems for illness and injury resulting from pathogens and chemical substances that are on CDC's critical agents list.
- Develop new algorithms and statistical methods for searching medical databases on a real-time basis for evidence of suspicious events.
- Establish criteria for investigating and evaluating suspicious clusters of human or animal disease or injury and triggers for notifying law enforcement of suspected acts of biological or chemical terrorism.

Diagnosis and Characterization of Biological and Chemical Agents

- Establish a multilevel laboratory response network for bioterrorism that links public health agencies to advanced capacity facilities for the identification and reporting of critical biological agents.
- Establish regional chemical terrorism laboratories that will provide diagnostic capacity during terrorist attacks involving chemical agents.
- Establish a rapid-response and advanced technology laboratory within CDC to provide around-the-clock diagnostic support to bioterrorism response teams and expedite molecular characterization of critical biological agents.

Response

- Assist state and local health agencies in organizing response capacities to rapidly deploy in the event of an overt attack or a suspicious outbreak that might be the result of a covert attack.
- Ensure that procedures are in place for rapid mobilization of CDC terrorism response teams that will provide on-site assistance to local health workers, security agents, and law enforcement officers.
- Establish a national pharmaceutical stockpile to provide medical supplies in the event of a terrorist attack that involves biological or chemical agents.

BOX 6. *(Continued)* Implementation Priorities Regarding Focus Areas for 2000–2002

Communication Systems

- Establish a national electronic infrastructure to improve exchange of emergency health information among local, state, and federal health agencies.
- Implement an emergency communication plan that ensures rapid dissemination of health information to the public during actual, threatened, or suspected acts of biological or chemical terrorism.
- Create a website that disseminates bioterrorism preparedness and training information, as well as other bioterrorism-related emergency information, to public health and health-care workers and the public.

RECOMMENDATIONS

Implementing CDC's strategic preparedness and response plan by 2004 will ensure the following outcomes:

- U.S. public health agencies and health-care providers will be prepared to mitigate illness and injuries that result from acts of biological and chemical terrorism.
- Public health surveillance for infectious diseases and injuries — including events that might indicate terrorist activity — will be timely and complete, and reporting of suspected terrorist events will be integrated with the evolving, comprehensive networks of the national public health surveillance system.
- The national laboratory response network for bioterrorism will be extended to include facilities in all 50 states. The network will include CDC's environmental health laboratory for chemical terrorism and four regional facilities.
- State and federal public health departments will be equipped with state-of-the-art tools for rapid epidemiological investigation and control of suspected or confirmed acts of biological or chemical terrorism, and a designated stock of terrorism-related medical supplies will be available through a national pharmaceutical stockpile.
- A cadre of well-trained health-care and public health workers will be available in every state. Their terrorism-related activities will be coordinated through a rapid and efficient communication system that links U.S. public health agencies and their partners.

CONCLUSION

Recent threats and use of biological and chemical agents against civilians have exposed U.S. vulnerability and highlighted the need to enhance our capacity to detect and control terrorist acts. The U.S. must be protected from an extensive range of critical biological and chemical agents, including some that have been developed and stockpiled for military use. Even without threat of war, investment in national defense ensures preparedness and acts as a deterrent against hostile acts. Similarly, investment in the

public health system provides the best civil defense against bioterrorism. Tools developed in response to terrorist threats serve a dual purpose. They help detect rare or unusual disease outbreaks and respond to health emergencies, including naturally occurring outbreaks or industrial injuries that might resemble terrorist events in their unpredictability and ability to cause mass casualties (e.g., a pandemic influenza outbreak or a large-scale chemical spill). Terrorism-preparedness activities described in CDC's plan, including the development of a public health communication infrastructure, a multilevel network of diagnostic laboratories, and an integrated disease surveillance system, will improve our ability to investigate rapidly and control public health threats that emerge in the twenty first century.

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MMWR™
MORBIDITY AND MORTALITY
WEEKLY REPORT

April 21, 2000 / Vol. 49 / No. RR-4

Recommendations and Reports

Continuing Education Activity Sponsored by CDC

Biological and Chemical Terrorism: Strategic Plan for Preparedness and Response Recommendations of the CDC Strategic Planning Workgroup

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GOALS and OBJECTIVES

This *MMWR* provides recommendations and guidance for initiating a national preparedness program for biological and chemical terrorism. The recommendations were developed by a workgroup with representatives from the Council of State and Territorial Epidemiologists, Association of State and Territorial Health Officials, and Association of Public Health Laboratories, with contributions from federal and professional organizations during a meeting held in August 1999. The goal of this report is to guide United States public health and medical preparedness efforts. Upon completing this educational activity, the reader should be able to identify a) criteria used to designate critical biological and chemical agents; b) five core focus areas for domestic terrorism preparedness; c) critical components of public health response to terrorism; and d) partners in an effective response to biological and chemical terrorism.

To receive continuing education credit, please answer all of the following questions.

1. Which of the following are good biological terrorism threats because of substantial morbidity and mortality, ease of production, efficient dissemination, stability in aerosol, or high infectivity?

A. Anthrax, chickenpox, botulism, and plague.

B. Anthrax, smallpox, chickenpox, and plague.

C. Anthrax, smallpox, botulism, and plague.

D. Anthrax, smallpox, mumps, and plague.

2. Biological weapons can be considered the ultimate weapon because they . . .

A. cause mass casualties.

B. are inexpensive and easy to produce.

C. can be difficult to detect.

D. can be disseminated at great distances.

E. all of the above.

3. Which of the following diseases have potential for person-to-person transmission?

A. Anthrax and plague.

B. Plague and botulism.

C. Botulism and brucellosis.

D. Smallpox and plague.

4. Which attribute does NOT determine whether or not a biological agent is included on the CDC critical agent list?

A. The agent's potential for causing morbidity and mortality to the public.

B. The agent's ability to cause disease in animals.

C. The agent's ability for dissemination to a large number of persons.

D. The need for special preparedness in response to the agent's release.

E. The likelihood of person-to-person transmission of an agent because of its release.

5. Which of the following would be included in a public health response to a biological terrorism event or any other disease outbreak?

A. Conducting a surveillance.
B. Investigating disease clusters.
C. Testing a hypothesis regarding transmission.
D. Evaluating control strategies.
E. All of the above.

6. Which of the following would NOT be considered a requirement for public health response preparedness for biological terrorism?

A. Stockpiling a national supply of vaccine, antitoxins, and medical equipment?
B. Vaccinating the civilian population for anthrax.
C. Creating a state emergency response plan for biological terrorism.
D. Establishing a surveillance system for critical biological agents.

7. Which of the following positions are responsible for evaluating or reporting a cluster of disease that is suspected to be the result of terrorism activity?

A. Epidemiologists.
B. Primary-care providers.
C. Laboratorians.
D. Emergency response personnel (e.g., emergency medical service, fire, or police).
E. All of the above.

8. Which of the following federal agencies has responsibility for crisis management during a biological or chemical terrorism event?

A. Internal Revenue Service.
B. Federal Bureau of Investigation.
C. Federal Emergency Management Agency.
D. Central Intelligence Agency.
E. Centers for Disease Control and Prevention.

9. Which of the following would NOT have a potential impact on the public health-care system in case of a biological terrorism event involving anthrax?

A. Fear and panic among the public.
B. Overwhelming number of casualties.
C. Overwhelming demand for intensive care modalities.
D. High potential for patient-to-provider spread of the disease agent.
E. Overwhelming demand for antibiotics.

10. Which of the following group(s) need to prepare and test a community emergency preparedness plan?

A. Public and private health-care providers.
B. Public safety officials.
C. Law enforcement personnel.
D. Elected officials.
E. All of the above.

11. A local preparedness plan should include which of the following?

A. Communication systems between state and local groups.
B. Testing mechanisms in laboratories.
C. Plans to triage and treat mass casualties.
D. Exercises to test community plans.
E. All of the above.

12. The key components of a national preparedness plan include which of the following?

A. Establishing response mechanisms.
B. Strengthening surveillance systems.
C. Strengthening laboratory systems.
D. Enhancing communications and training.
E. All of the above.

13. Indicate your work setting.

A. State/local health department.
B. Other public health setting.
C. Hospital clinic/private practice.
D. Managed care organization.
E. Academic institution.
F. Other.

14. Which of the following best describes your professional activities?

A. Patient care — emergency/urgent care department.
B. Patient care — inpatient.
C. Patient care — primary-care clinic.
D. Laboratory/pharmacy.
E. Administration.
F. Public health.

15. I plan to use these recommendations as the basis for . . . (Indicate all that apply.)

A. Health education materials.
B. Insurance reimbursement policies.
C. Local practice guidelines.
D. Public policy.
E. Other.

16. How much time did you spend reading this report and completing the exam?

A. 1–1½ hours.
B. More than 1½ hours but fewer than 2 hours.
C. 2–2½ hours.
D. More than 2½ hours.

17. After reading this report, I am confident I can identify criteria used to designate critical biological and chemical agents.

A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

18. After reading this report, I am confident I can identify five core focus areas for domestic terrorism preparedness.

A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

19. After reading this report, I am confident I can identify critical components of public health response to terrorism.

A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

20. After reading this report, I am confident I can identify partners in an effective response to biological and chemical terrorism.

A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

21. The objectives are relevant to the goal of this report.

A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

22. The text boxes and figure are useful.

A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

23. Overall, the presentation of the report enhanced my ability to understand the material.

A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

24. These recommendations will affect how I conduct or participate in biological and chemical terrorism preparedness planning.

A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

Correct answers for questions 1–12

1. C; 2. E; 3. D; 4. B; 5. E; 6. B; 7. E; 8. B; 9. D; 10. E; 11. E; 12. E.

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April 21, 2000/Vol. 49/No. RR-4

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Recommendations of the CDC Strategic Planning Workgroup

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Fill in the appropriate blocks to indicate your answers. Remember, you must answer <u>all</u> of the questions to receive continuing education credit!

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5. [ ] A [ ] B [ ] C [ ] D [ ] E
6. [ ] A [ ] B [ ] C [ ] D
7. [ ] A [ ] B [ ] C [ ] D [ ] E
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23. [ ] A [ ] B [ ] C [ ] D [ ] E
24. [ ] A [ ] B [ ] C [ ] D [ ] E

Signature ***Date I Completed Exam***

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